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VOLUME 4

CLINICAL CARDIOLOGY—THERAPY

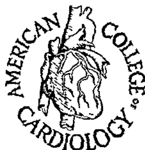
CARDIOLOGY

An Encyclopedia of the Cardiovascular System

SPONSORED BY THE AMERICAN COLLEGE OF CARDIOLOGY

EDITED BY ALDO A. LUISADA, *M.D.*

FOREWORD BY ASHTON GRAYBIEL, *M.D.*



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CARDIOLOGY

An Encyclopedia of the Cardiovascular System

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Foreword

This work is at once a landmark in clinical cardiology and an indication of the Golden Age of Medicine in which we now live. Because wondrous things have become commonplace, we can appreciate this age only in retrospect. From rude beginnings it is possible to trace, over the centuries of recorded history, the gradual refinement in skills, the slow accumulation of factual knowledge, and the emergence of a scientific discipline so essential to success in the walks of science Progress, painfully slow and often faltering till late in the nineteenth century, then began to accelerate at an ever-increasing rate. Within the memory of some now living, individual triumphs in scattered departments of science combined in one mighty triumphant flourish to usher in the modern era. Epidemics, once the scourge of man, were abolished, certain diseases, once relentless in their course, were controlled, old age, once a rarity, became the rule. It is unlikely that within a comparable period of time man will ever again repeat the stupendous feat of doubling his span of life.

Cardiologists, while sharing in these triumphs, saw heart disease assume the lead as a cause of death in many countries. Thus, although gratified by the increased longevity of man, we are nevertheless challenged by the disclosure that the cardiovascular system is now the weakest strand in the thread of life. Indeed, its relative importance in the lives of men appears destined to increase, for there is nothing in sight pointing to a major break-through in the prevention of heart disease in old age.

In sponsoring this encyclopedia, the American College of Cardiology, dedicated to the continuing education of its membership, is simply fulfilling one of its obligations That this particular obligation weighed more heavily on the minds of some of its officers than on others raised the question of the relative merits of different methods of postgraduate education. We cannot here record the deliberations which finally led to approval of this undertaking, but they reflected the need for putting on record the widening horizons of our knowledge of cardiovascular disease

That the presentation of information concerning the heart and circulation requires four volumes involving upwards of 250 authors has important implications. It is evidence that narrowing of interest and progress go hand in hand, and that subdivision within the field of cardiology is well established But this subdivision, so essential for progress, must be reconstituted for those whose clinical responsibilities cover a broad area In effect this encyclopedia represents such a reconstitution. It contains authoritative information abstracted from an immense mass of medical literature which could not be reviewed effectively by an individual The organization of this material is based on a logical framework

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Preface

This work was started as a result of a bold and far-sighted initiative of Dr. Ashton Graybiel, then president of the American College of Cardiology.

The task of editing an encyclopedia of cardiology represents a challenge which is both appealing and frightening.

Among the multitude of books of cardiology which have been published in the last 20 years, the majority belongs to the type of the medium-sized, monographic textbook written by a single author. A few have been written in collaboration by several authors. These, however, do not attempt to be complete and are, moreover, too unsystematic to be helpful. Being of the "fixed-volume" type, they are soon outdated and, therefore, forgotten

In ancient Greece, *encyclopaedia* meant "instruction in the whole circle, or complete system of learning" In a more restricted sense, encyclopedia means "a system or classification of various branches of knowledge, a subject on which many books have been published." While many encyclopedias of the past have been of the "alphabetical type" (each word to be explained is listed in alphabetical order), others have tried to reconcile system with completeness Thus, even in the early editions of the *Encyclopaedia Britannica*, the various sciences and arts (such as anatomy or surgery) were "digested into distinct treatises or systems" On the other hand, technical terms were explained in alphabetical order. Older encyclopedias, like Plinius's *Natural History* of the year 77 A.D. (37 books with 2,493 chapters) or *Yung-Lo Ta Tien*, the Chinese encyclopedia of 1403 A.D. (11,095 volumes prepared in four years by over 2,000 scholars), were developed according to system. The latter even included well-known books reproduced without change

In the opinion of the editor, a modern encyclopedia of cardiology ought to have the following characteristics. (1) It should encompass all available knowledge on the heart and vessels, including history, embryology, anatomy, physiology, physical and technical methods of examination, bacteriology and pathology, clinical sciences, surgery, pharmacology and therapy, rehabilitation, and the various "allied fields." (2) It should present them in a systematic order, thus permitting easy consultation (3) It should be of the loose-leaf type, in order to keep abreast of medical progress It is then possible that some of the readers may prefer to call this a *treatise*

The principle of extending the work to all kinds of knowledge in the cardiovascular field should not be carried too far in the marginal fringes of medical or technical sciences. This process would divert and distract the attention of the reader and would render consultation too difficult. Therefore, a process of selection and limitation is an important part in the preparation of an encyclopedia of

which constitutes a resynthesis of the important elements in the field of cardiology.

In using this encyclopedia, the physician must let go of his inclination to be taught, and cultivate the art of selecting new items of information and fitting them into a frame of reference dictated by his needs. This method does require a capacity for mental independence and is effective only in so far as this is exhibited by those for whom the encyclopedia is intended. Admittedly a work of this sort represents a form of communication in which there is much redundancy. At what point will the evil of redundancy equal or exceed the good contained in the message? Herein lies a very real problem with which we should be concerned in the future.

It is noteworthy that in the compilation of this work we are more dependent upon an editor than upon an author. The choice of Dr. Luisada to edit the work has been fortunate. He has exhibited not only a natural talent for this task but also the quality of persevering in the face of difficulties. To him alone belongs the credit for bringing the encyclopedia to fruition The present handbook must be regarded as a monument to his genius.

ASHTON GRAYBIEL

2. Selection of persons with diversified knowledge (physiology, pathology, pediatrics, surgery, etc.), so that all fields may be covered by competent editors.

3. Choice of as many young scientists as possible, in order to have a high potential of enthusiasm, criticism, and working capacity.

The final product will reveal whether these directives are sound and have been followed as closely as possible.

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ALDO A. LUISADA
Editor in Chief

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The problem of correlation has been the rock on which many textbooks written by multiple authors have foundered. If the various parts do not follow a logical sequence; if some of them are disproportionately long or short; if some are written by obscure authors of poor talent while others are the result of the work of well-known authorities; then the whole encyclopedia has no value.

In order to obviate these possibilities, the following steps are necessary: (1) the authors selected should be among the best, (2) each should receive a carefully selected and clearly outlined job, and (3) the editors should be able to refuse, abbreviate, or send back for correction any received text. Therefore, courage, patience, and hard labor are necessary to ensure a successful literary production.

The outcome of the work depends to a large extent upon the selection of authors. Well-known authors who have left a mark in the history of cardiology are the natural choice. However, they may be reluctant to undertake a major task and, moreover, may not be able to ensure continuity on account of their age. A compromise may be represented by asking these authors to prepare the text in collaboration with one of their associates. The associate would be the natural choice for any future revision of the text. However, a different author may entirely revise a chapter at a future date.

Science is international. If a truly objective work is to be published, authors of all nationalities should be asked to contribute. The recent tremendous progress of cardiology in the North American continent may require that a majority of the authors be selected in the United States and Canada However, numerous contributors have been selected from England, continental Europe, Mexico, South America, Africa, and Asia, so that a truly "global" representation of cardiology may result.

How much of the text should reflect generally accepted viewpoints; how much should present new ideas still awaiting confirmation? This problem cannot be solved in a general way. The viewpoint of the editor is that an intermediate position should be preferred. Texts reflecting only generally accepted views might render the entire work obsolete within a few years. On the other hand, many new viewpoints cannot withstand the test of time and are gradually discarded. Whatever the error, whether in the sense of conservatism or in that of progressivism, a loose-leaf type of work may remedy it more rapidly than any standard type of volume.

The Editorial Board has been selected with great care according to these viewpoints:

1. Inclusion of a few authorities which would help in laying down the directives of the work.

2. Selection of persons with diversified knowledge (physiology, pathology, pediatrics, surgery, etc.), so that all fields may be covered by competent editors.

3 Choice of as many young scientists as possible, in order to have a high potential of enthusiasm, criticism, and working capacity.

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PART 12

Hypertension and hypertensive heart disease

PART 12

Hypertension and hypertensive heart disease

1

The range of normal blood pressure

BLAS MOIA

The values of normal arterial pressure undergo notable modifications during the course of life and according to the mode of life of each individual

In the healthy *new born*, the average arterial pressure is around 55/40 mm Hg (Bricker and Connell) but rises rapidly in the days following birth Reis and Chaloupka observed that the systolic pressure rose from an average of 43 mm during the first day of life to 78 mm at the age of 10 days, the greatest elevation apparently occurring during the first 3 days Between the first month and the first year of life, the pressure continues to rise, although not so rapidly, attaining an average of from 59/30 to 95/58 mm Hg at the end of the first year of life From 5 to 16 years of age, the average pressure values are from 92/52 to 122/62 mm From this point on, opinions begin to differ. Some authors, especially Alvarez et al, find a marked elevation during *puberty and adolescence*, followed by a diminution in later years, the average systolic pressure being 127 mm at 16 and 118 mm at 30 in males, and 118 mm at 16 and 111 mm at 24 in females The greater rise in men could perhaps be explained by the fact that boys mature between the ages of 16 and 19 and are stronger and more active at that age than girls, who mature at an earlier age

Nevertheless, recent statistics (such as those of Master et al. and Hamilton et al), based on more exacting techniques of pressure registration, do not confirm the existence of such variations They show that after the age of 16, the average arterial pressures, systolic as well as diastolic, continue to rise slowly and regularly with age, although after 50 years of age the systolic pressure rises more rapidly. This point is illustrated in Table 12-1 from Master et al., made with measurements taken in 15,700 persons of both sexes between the ages of 16 and 65, selected at random among 74,000 industrial workers. The average figures are somewhat lower than those of Goldberg and of Russek et al., and a little higher than those of Robinson and Brucer, although the figures are practically parallel

In the elderly individual, especially after 65 years of age, the average systolic pressure is *above 150 mm Hg*, arriving at around 165 mm between the ages of 85 and 95. However, the variations of the diastolic pressure are much *smaller*, the average being 90 mm The changes are probably due to atherosclerosis of the aorta Nevertheless, Master et al., studying elderly persons without evidence of cardiovascular disease, find that the average systolic pressure does not continue to rise in males after the age of 65 or in females after the age of 70 The pressure remains constant until the age of 85 and then declines Between the ages of 70 and 74, the average values were 14 mm higher in women than in men, tending to become equal at the age of 90 In contrast, the diastolic pressure shows no difference in regard to sex and falls slightly after the age of 85.

It is evident that the behavior of these variations of pressure is influenced by sex as well as by age Indeed, with a few discrepancies, almost all statistics show that, until around the age of 40, the arterial pressure, and especially the systolic pressure, is somewhat lower

TABLE 12-1. SYSTOLIC AND DIASTOLIC PRESSURE READINGS BY SEX AND AGE

Sex and age	*Systolic*			*Diastolic*		
	Mean	*Standard deviation*	*Coefficient of variation*	*Mean*	*Standard deviation*	*Coefficient of variation*
Males:						
16	118 4	12.17	10.28	72.9	10.33	14.17
17	121.0	12 88	10.64	74.4	9.36	12.58
18	119.8	11.95	9.97	74.4	10.03	13.48
19	121 8	14.99	12 31	74.6	10.29	13.79
20–24	122 9	13 74	11.18	76.0	9.93	13.07
25–29	125.1	12 58	10.06	77 8	8.98	11.54
30–34	126.1	13 61	10.79	78 5	9.68	12.33
35–39	127.1	14.20	11 17	80.4	10 42	12.96
40–44	129 0	15.07	11.68	81 2	9.53	11.74
45–49	130 0	16.93	13 02	82.0	10.81	13.18
50–54	134.5	19.21	14.28	83 4	11 31	13.56
55–59	137.8	18.80	13 64	84.0	11.40	13.57
60–64	141.8	21 11	14.89	84.5	12.36	14.63
Females:						
16	116 1	12.10	10 42	72.3	9.55	13.21
17	116.0	11 51	9.92	72.0	9 16	12.72
18	116.3	11 42	9.82	71.8	8.60	11.98
19	115.1	11 87	10 31	71.1	8 93	12 56
20–24	115.7	11 83	10 22	71 7	9.67	13.49
25–29	116 8	11 43	9.79	73 7	9.05	12.28
30–34	119 8	13 97	11 66	74 9	10 78	14.39
35–39	123.9	13 85	11 18	78 0	10.01	12.83
40–44	127.0	17.07	13.44	79.5	10.60	13.33
45–49	130 6	19.47	14 91	81 5	11 63	14 27
50–54	137 3	21.29	15 51	83 5	12.36	14.80
55–59	138.5	21.40	15.45	83.5	11 72	14.04
60–64	144.0	22.33	15.51	85 0	12.95	15.24

SOURCE: Master et al.

in females than in males, while later it tends to become somewhat higher, although without significant differences. It must be noted that this rise in arterial pressure according to age does not present the same degree in all individuals. *There are persons in whom the pressure rises very little during different decades of life*, presenting, even in old age, relatively low figures (for example 120/70), while others may have a rapid rise and may have values in excess of 150/100 mm Hg at the age of 50

There have been attempts to explain these differences in the behavior of arterial pressure on the basis of constitutional, racial, environmental, and other factors, but no definite conclusions have been drawn on this subject Indeed, other than genetic and hereditary factors, which seem to be well substantiated, there is very little agreement on the numerous other elements which have been postulated For example, no one has been able to demonstrate the existence of a definite psychic hypertensive personality *Stress*, which has been accepted as an etiologic factor of hypertension by some investigators, is not accepted by the majority. There does not seem to be convincing evidence that *occupation* per se and *environmental physical factors* play a significant role in the elevation of arterial pressure.

The importance of the *racial factors*, especially in reference to the characteristics of the pressure behavior in Negroes of different countries, Chinese, etc., cannot be seriously considered until new statistics have been tabulated with uniform criteria and taking into consideration state of nutrition, body weight, etc.

It is quite evident that blood pressure tends to be higher in persons of heavy build. According to the statistics of Master et al., the difference in the average systolic pressures between very light and very heavy individuals is greater than 10 mm, the diastolic pressures following an almost parallel course. These differences are more notable in females, particularly after the age of 40. On the other hand, they do not have any relationship with the *height* of the individuals.

These variations may or may not have real significance, but it is important to decide when the values found for a determined age cease to be physiologic and become pathologic The anarchy which reigns with respect to the evaluation of all these factors is impressive Table 12-2, based on a careful analysis of 33 publications, gives an idea of the situation Adding still more to the confusion is the difference in criterion of different authors in regard to the reading of the diastolic pressure, technical errors, etc.

Obviously one of the least acceptable criteria is the evaluation of the systolic pressure only There may exist an abnormal increase in the systolic pressure with a normal or low diastolic pressure; this may occur without hypertensive disease (i e., without increase in peripheral resistance), in aortic insufficiency, hyperthyroidism, complete AV block, and atherosclerosis of the aorta and its large branches However, in the latter condition, there may be a rise in the diastolic pressure, although generally less marked On the other hand, an abnormal rise in diastolic pressure in rare cases may not be accompanied by a systolic rise, and should be considered as evidence of arterial hypertension

It is widely accepted that the upper limit of norm is 150 mm Hg for the systolic pressure and 90 mm for the diastolic, but this absolute dividing line between normal and abnormal pressures cannot be considered as valid any longer It is evident that a figure of 150/90 would be much more abnormal for a girl of 20 than for a woman of 50 It is necessary then to allow a greater elasticity to this dividing line and to consider as normal not only what is most perfect, but also *what is the most frequent* For example, we do not frequently find definitely elevated blood pressures in the young individual and, therefore, in such a circumstance any elevation should be considered as indicating a secondary hypertension. On the other hand, figures of 140/90 or even more are found (Master et al.) in 40 per cent of individuals between the ages of 45 and 49, and in 60 per cent of persons between 60 and 64. Figures around 150/100 or more are found in 20 per cent of individuals between 40 and 45 and in 35 per cent of those from 60 to 64.

Pickering (1955b), whose statistics support the concept of Master et al., believes that the differences between the highest and lowest pressures are quantitative and not qualitative; there are differences of degree and not types. Consequently, there cannot be "justification for a division of arterial pressures into normal and pathologically high, and it is the height of the pressure that matters." Sharing this opinion are Kagan et al., who, after reviewing results of the first 4,499 carefully studied cases in Framingham, state that "there was no evidence in the distributions or in the correlations with x-rays and electrocardiographic abnormalities to suggest a sharp line of demarcation between normal and abnormal blood pressures" These concepts, interesting as they may be, should nevertheless be considered with caution. They demonstrate the distribution of pressure values in men and women of different groups according to age but *do not exclude that this large percentage of individuals, whose*

TABLE 12-2 CRITERIA USED FOR CLASSIFICATION OF PERSONS AS HYPERTENSIVE IN 33 STUDIES OF BLOOD PRESSURE

Level dividing normal from abnormal, mm, Hg	*No of studies*
150/90	4
120/80	1
Diastolic 100	3
Systolic 145	1
155/95	1
Systolic 150	6
Systolic 140	8
Diastolic 90	3
150/95	2
Under 40 years, 140/90; Over 40 years, 150/90	1
Systolic 160	1
150/100	1
Systolic 143	1
Total	33

SOURCE. Morsell.

arterial pressure tends to be greater than 140/90, are actually moderately hypertensive and do not indicate with certainty that they are simply presenting the result of a physiologic aging process In order to overcome this objection, Master et al. suggest considering as abnormal *the sum of the mean values plus the double of the standard deviation,* but this criterion, although statistically acceptable, is arbitrary, since there is no sharp division between the levels of clearly normal and clearly abnormal pressures. Therefore, it is necessary to complement the criteria of frequency with those of morbidity and mortality, and to try to find for a determined age group which pressure levels correspond with persons who have not developed clinical manifestations of hypertensive disease or arteriosclerosis and who have no decrease of their life expectancy This study would be more important from a medical and a social viewpoint but is very difficult to translate into reality Everyone who has been able to follow the evolution of hypertensive individuals for more than 20 or 25 years has seen patients with very high blood pressures who continue to live with few or no clinical manifestations while others, with less marked pressure elevations (sometimes below 180/110), rapidly suffer the consequence of hypertensive disease and die as a result of its complications

The statistical studies of insurance companies demonstrate an increase in mortality as soon as the pressures begin to rise, even if only to a slight degree, above the limits which are now commonly accepted as normal But this criterion, useful from their viewpoint, is not necessarily indicative that the increase in mortality is a direct consequence of the pressure rise, since they do not take into consideration the morbid factors which have contributed to this rise and which may themselves be responsible for death The importance of the vascular disease which usually accompanies, but may not be secondary to, the blood pressure rise should not be neglected

Even admitting the existence of these exact demarcation levels, the situation is complicated by the fact that many persons, without going beyond the maximum limits which are commonly considered as normal, have pressures which are high for their age. Others, whose hypertension is of the so-called "labile" or "transitory" type, may be, under certain circumstances, above or below the normal limits Such variations in pressure may be observed during a single physical examination in which the reading is repeated at brief intervals or in examinations done at different hours of the day or on different days and under different circumstances. Since the observations of Addis, it has been customary to call *basal pressure* that which is found as soon as the patient awakens and before he arises from bed or takes food. According to Alam and Smirk, "basal pressure" is the pressure found in conditions similar to those in which a basal metabolism test is done, while *casual pressure* is that found without previous preparation and during the normal daily activities. The difference between basal pressure, which is always lower, and casual pressure, represents the supplementary fraction which depends upon emotional stress, physical activity, or suprabasal metabolic activity of the patient in a given moment

The significance of these findings in regard to their relation to normal arterial pressure range has not yet been properly clarified Some authors consider that fluctuations of less than 15 to 20 mm Hg due to physical fatigue are normal and physiologic. On the other hand, others believe that short periods of sustained elevation of the arterial pressure should be considered as early manifestations of hypertensive disease

The Anglo-American Committee on Standardization of Blood Pressure Readings, in its first report, warns against reaching any definite conclusion in regard to the blood pressure of any individual unless numerous pressures have been taken in successive visits, because frequently the first reading is much higher than the following, owing to the patient's apprehension and nervousness. Smithwick, as well as Perera, insists on the necessity of taking basal pressures for statistical studies. "The arterial pressure, as it is casually recorded is of little significance in determining trends or prognosis" Nevertheless, this criterion is not without fault there are patients with obvious clinical evidence of hypertensive disease who, after some days or weeks of bed rest, and especially if they are isolated from their usual

environment, have such a marked lowering of both casual and basal pressures as to be found normotensive.

It is probable, although not definite, that arterial hypertension is less reversible in patients whose pressure elevations are more fixed. But, although it is evident that the level of arterial pressure is not the only factor which determines the severity of the hypertensive process, it cannot be denied that the casual hypertension which the patient suffers during at least 14 to 16 hr during the day, should have unfavorable repercussions on his circulatory system, even though the pressure becomes normal during rest.

The most valuable information with respect to the significance of this transitory type of hypertension is that given by statistics gathered by Levy et al (1944), based on pressure readings of 22,741 officers of the U.S. Army, 84 per cent of whom were under observation for 5 to 19 years, 38 per cent from 15 to 19 years, and 6 per cent for 20 years or more. Only those patients were considered whose first examination revealed a pressure of 150 mm or more systolic and at least 90 mm of diastolic pressure, but in whom was found a pressure drop either during the same or in a subsequent examination It was observed that the frequency of these exaggerated pressure variations increased with age, following a uniform line which began with 5 9 per cent between the ages of 25 and 29 and ended in a plateau with 18 6 per cent between the ages of 50 to 54 The age group percentages of persons in this group who developed permanent hypertension varied between 2 4 per cent between the ages of 25 to 29 and 48 per cent between the ages of 55 to 59, in contrast to 0 to 5 per cent and 14 9 per cent respectively for the control group

It may be said that permanent arterial hypertension develops 3 5 times more often in individuals with labile or transitory hypertension than in others It is interesting that the development of a permanent arterial hypertension was observed both in cases with small pressure fluctuations and in cases with large ones. In this sense, it is significant that even a slight, isolated systolic hypertension or a transitory rise of the diastolic pressure above 100 mm is the forerunner of permanent arterial hypertension Later, these same authors observed that, in addition to transitory hypertension, tachycardia and excessive body weight are important in the development of a permanent hypertension, the *probabilities increasing if* two of these factors exist together and especially if all three are found present Nevertheless, Hines (1940), discussing the significance of pressor tests, reaches the conclusion that the type of hyperreaction which is accompanied by tachycardia and *systolic hypertension*, and which is due basically to an increase in cardiac output, is not characteristic of arterial hypertension in any of its states. On the other hand, that which is accompanied by *diastolic hypertension* (with or without systolic hypertension) and without significant tachycardia, apparently predicts the *development of* a sustained arterial hypertension in more than 50 per cent of the cases.

In regard to the already mentioned statistical data, there are contradictions which *depend* not only upon the *different criteria of interpretation* of each author but also on the different conditions and methods of examination used. Nevertheless, *considered as a whole*, these statistics *clearly indicate that an absolute line of demarcation cannot be fixed between normal and abnormal blood pressure in man* Therefore, each case should be considered individually, taking into account not only the clinical picture, but all the above-mentioned factors which may be acting.

Although hypertension is only a *sign of the* disease as long as *the cause* is not known, one must be guided by pressure readings in order to judge if a hypertensive state exists or not. There is no doubt as to the definition of normal or abnormal if two adult individuals present arterial pressures of 120/80 and 200/120, *respectively*. On the other hand, doubt may arise when, as the person advances in age to about 50, it is found that he has permanent or transitory readings oscillating in the borderline zone around 150/100 *If, at this time*, an exhaustive clinical examination of the patient does not provide other *evidence* of hypertensive disease, it is wise not to consider him hypertensive, as yet Although *it is* more common that persons of this group develop in time more significant hypertension, it is not necessarily *always* true that an individual in

the group will do so. It is evident that there is a high percentage of patients who for many years remain free of vascular and visceral complications while their pressure level does not rise significantly, and the life expectancy is not shortened. Consequently, before labeling one of these patients "arterial hypertensive," with all the unhappy psychologic effects which may follow, the physician should submit his patient to a careful and prolonged clinical observation, advising him as to the most appropriate mode of life but without subjecting him to uncomfortable or harmful restrictions or unnecessary therapeutic measures.

2

Psychic factors in essential hypertension

PHILIPPE V. CARDON, JR.

Before considering the psychic factors involved in hypertension and hypertensive heart disease, it is advisable to ask what is meant by psyche and psychic factors

BASIC CONCEPTS

The function of all living *organisms can be* altered by changes in the environment Organisms with well-developed central nervous systems often perceive environmental changes at a distance with the organs of sight, hearing, and smell The brain then decides whether something should be done about them If so, heretofore minute physical changes within the organisms, induced in the brain by the environmental changes, may trigger gross *energy* transformations in other parts of the body Whether the brain's evaluative function is "thinking" or "instinct," "conscious" or "unconscious" is irrelevant here The entire sequence consists only of physical (material) phenomena The word "psyche" is a useful abstraction to denote an aspect of the brain's physical function, just as "circulation" denotes the function of heart and blood vessels The word "psychosomatic" is clear in its *intent* but inaccurate in its implication that the psyche is not part of the soma

It is well established that the brain (psyche) can cause changes in the functions of the rest of the body through three mediating systems the nerves to skeletal muscles, the autonomic nervous system, and the endocrine system "Psychosomatic" inquiry tries to define and quantify these changes in man and to define their relevance, if any, to disease and death

Historically, interest has focused primarily on the bodily changes that occur in psychically troubled people. Changes postulated to be harmful to them are usually thought of as inappropriately sustained emergency responses—inappropriate in the sense that such individuals habitually perceive minor challenges as serious threats. However there is [illegible]

[illegible] everyday life as harmless Neither can one assume that physiologically harmful adjustments to environmental stimuli necessarily stem from "sick," "abnormal," or "neurotic" interpretations of the stimuli.

A minority of "psychosomatic" phenomena are best explained as symbolic expressions of feelings or impulses, presumably unconscious makeshift "solutions" of neurotic conflicts. *The majority, of which acute neurogenic hypertension is an example, cannot be satisfactorily explained in this way* They are phenomena of which the psyche *is completely* unaware They frequently seem to make more sense viewed as *manifestations of adjustments* which have favored *survival* of the species during evolution Such a *view does not* necessarily imply that the adjustments *promote* good health beyond the child-bearing *years, that they* are useful in civilized life, or that *epiphenomena* of useful adjustments are useful per *se*

PERSONALITY AND BEHAVIOR

It has been the usual experience of psychiatrically oriented investigators that as a group [illegible]

[illegible] Weiss et al). Patients have been characterized by different observers as having neurotic traits, excessive dependency needs, poorly handled feelings of hostility, difficulties in interpersonal relationships, excessive rigidity, etc They tend to be less assertive, less at ease and more uncertain in their relationships with other people, easily *injured* but fearful of hurting others. Efforts *to* define a

characteristic "personality profile" always and exclusively present in patients with hypertension have been unsuccessful. Some observers reporting group differences also report a small minority of hypertensive patients who, by the same criteria, have normal personalities.

That chronic illness of any sort may accentuate latent personality defects probably does not account for the observed differences. In one study, hypertensive persons were matched with neurotic patients without hypertension or other of the disorders commonly termed "psychosomatic," and with patients with chronic "nonpsychosomatic" diseases, such as malignancy, anemias, chronic pulmonary infection, etc. Each group was rated as to the extent to which the traits of anxiety, hysterical symptoms, obsessive-compulsive behavior, depression, subnormal assertiveness, and impulsiveness were thought to be present By these criteria, *the entire group of hypertensive persons differed significantly from neurotic patients in that obsessive-compulsive and subnormal-assertiveness traits were more prominent.* They differed from the patients with other chronic illnesses in greater prominence of all traits except impulsiveness There was no significant difference among hypertensive patients with "neurogenic," "renal," or "endocrine" hypertension (Saslow et al)

Retrospective histories, which, of course, cannot be accepted at face value, usually indicate that the personality features antedate known hypertension Two separate studies showed that college students whose blood pressure was high on routine physical examination differed significantly in some personality features from those with low blood pressure (Hamilton; Harris et al.). These studies were suitably controlled and any bias of foreknowledge was eliminated. In the latter study, the psychologic criteria which enabled the investigators correctly to predict a subject's blood pressure category with significant frequency were derived from clinical experience with hypertensive patients. If such young people are more likely to develop essential hypertension, it follows that detectable differences in personality antedate the onset of hypertension. Studies like those cited do not establish a causal relationship between the psychic features observed and essential hypertension.

SYMPTOMS, SIGNS, AND OUTCOME

Most of the early symptoms of essential hypertension—headache, dizziness, fatigue, insomnia, musculoskeletal pain, exertional dyspnea, etc—seem definitely to be affected by psychic factors. Early observers pointed out the similarity between these symptoms and those encountered in patients with psychoneurosis (Riseman et al.; Ayman et al., 1931). The frequent lack of correspondence between symptoms and blood pressure level is well known At least half of hypertensive patients report the disappearance or lessening of these symptoms upon the establishment of a supportive relationship with the physician, despite the persistence of high blood pressure.

Variations in blood pressure level can frequently be correlated with variations in a patient's life situation Times of strained relationships with other people, particularly when the patient is continually angry, seem most often associated with rises in blood pressure. Periods of relative tranquility are often associated with lower blood pressure It is obviously difficult to control adequately such observations. It is doubtful whether reported studies can settle this question in the physician's mind any more effectively than his own clinical experience.

The *course* of hypertensive disease is probably often significantly modified by psychic factors The return of blood pressure to normal can reasonably be regarded as a favorable alteration of the course, and the development of the malignant phase as an unfavorable acceleration. As to *improvement*, in one psychiatrically oriented medical treatment program, in which antihypertensive drugs were not used, blood pressure returned to normal in about 10 per cent of patients (Wolf et al). These patients were considered, in retrospect, to have succeeded in making favorable basic alterations in their manner of dealing with life's problems More convincing, at the start of treatment, it had been predicted, on the basis of a prognostic index almost entirely psychologically and sociologically derived, that these particular patients would do well As to *worsening*, in a study of 12 patients who developed grade 4 retinopathy, it was concluded that in all patients the malignant phase was immediately preceded by, and continued to

develop in, life situations that were particularly difficult and threatening (Reiser et al). Furthermore, in some cases, resolution of difficulties was accompanied by a fall in blood pressure and disappearance of papilledema.

MECHANISM

What sorts of responses to psychic stimuli are similar to conditions present in resting hypertensive persons? The following brief discussion is a statement of the author's views on the significance of available data.

Hemodynamic Changes The blood pressure usually rises in response to psychic challenge or threat. Mean blood pressure may rise as much as 50 mm Hg within 30 sec In normotensive persons, the average rise is about 10 mm Hg, in hypertensive patients, about 18 mm Hg Expressed as percentage of [illegible] than systolic

Such acute rises are mediated principally by the sympathetic nervous system and adrenal medulla The rise is usually a result of *increased cardiac output with a fall in total peripheral resistance ("output" pattern)* Heart rate and flow to skeletal muscle increase, effective renal plasma flow decreases (by as much as one-third), as does flow to the skin of the extremities This type of pressor response is similar to that observed after moderator nerve interruption in man, after administration of epinephrine, and in frightened animals (Cannon's "fight-or-flight" response)

Though it occurs most frequently, this is not the only hemodynamic pattern in acute neurogenic hypertension Peripheral resistance may rise concurrently, and in less than one-third of instances the psychically induced rise in blood pressure is caused *solely by increased peripheral resistance ("resistance" pattern)* Cardiac output, pulse, and skeletal muscle blood flow do not rise (or may decrease), while flow to the kidneys and extremity skin decreases as usual Infusion of norepinephrine or electrical stimulation of certain areas in the frontal and temporal lobes of the cerebral cortex produces a similar pattern

In both patterns, the average rise in blood pressure is of about the same magnitude, as is the decrease in renal plasma flow, which usually persists for an hour or more after the blood pressure has returned to normal.

Naturally occurring output and resistance patterns are not such distinct entities as the artificial analogues induced by infusing epinephrine or norepinephrine For instance, neither hormone alone causes both cardiac output and resistance to increase—a not unusual natural occurrence. The frequent fall in diastolic blood pressure caused by epinephrine and the bradycardia caused by norepinephrine are rarely observed during psychic pressor responses.

The foregoing considerations indicate that the hemodynamic situation during acute neurogenic hypertension may closely resemble that seen in resting hypertensive patients. It is probably incorrect, however, to view essential hypertension as an inappropriately sustained neurogenic response of the resistance type For instance, hypertensive patients frequently respond to psychic stimuli with output patterns. Though some studies disagree, in the largest reported series, normotensive and hypertensive persons do not differ in pattern frequency (Wolf et al)

In the cold-pressor test, similarly, the more frequent pattern is of the output type in both normotensive and hypertensive persons. If an excessive rise in blood pressure in response to pain indicates a predisposition toward essential hypertension, there is no present basis to believe that resistance reactors are more or less vulnerable than output reactors

There is better evidence, which need not be detailed here, that the high peripheral resistance in established essential hypertension is maintained, at least in part, by factors other than increased sympathetic activity The most direct evidence of this to date is that about two-thirds of hospitalized hypertensive patients do not excrete excessive amounts of epinephrine or norepinephrine in the urine, while about one-third of them do (von Euler et al) The untested possibility remains that in everyday life, most hypertensive persons, rather than a minority of them, undergo unusually frequent and sustained episodes of sympathetic discharge for psychologic reasons and that, over a period of years, these episodes in turn result in the activation of other pressure-sustaining mechanisms

Changes in Vascular Reactivity. The conjunctival vessels of hypertensive patients are unusually sensitive to the constricting action of topical epinephrine and norepinephrine (Lee et al). In normal persons, sensitization can be induced acutely by psychic stimuli, and has been observed during the resting state on days when the subject's life situation was unusually trying (Ostfield et al) It is not known whether the mechanism of sensitization in the three circumstances is the same.

Changes in Renal Function. The role of altered renal function in the pathogenesis of hypertension is still unclear It is not known whether the neurogenic renal vasoconstriction which may follow

psychic stimuli can activate any of the several renal mechanisms suggested. There is some information, however, on the effects of psychic factors on water and sodium excretion The relevant reported abnormalities in hypertension are in the direction of the retention of water and sodium. Psychic factors often cause water and sodium retention.

THERAPEUTIC CONSIDERATIONS

The clinical and experimental information briefly reviewed above is incomplete and inconclusive Though many observers would prefer to reserve judgment pending better evidence, the practicing physician cannot do so, his patients need treatment *now* It seems more likely than not that psychic factors significantly contribute to the genesis and affect the course of essential hypertension, if so, what can one do about it?

It is possible that any benefit conferred by sympathectomy, ganglionic blocking agents, or centrally acting drugs, such as *reserpine* and *Apresoline,* results from a partial insulation of the psyche, either from the environment or from the rest of the body Certainly, the services provided by the physician (diagnosis, explanation, treatment, continued interest and support) are also potent and direct forms of psychotherapy. The question arises whether some more explicit effort is worthwhile to help the patient to think and act differently While many patients and physicians are convinced that it often is, acceptable scientific validation of this conviction does not exist as yet. The following suggestions are offered to physicians because they seem reasonable in the light of present knowledge.

Initial Evaluation. At your first contact, begin to look for clues to the question, "What *sort of a person* is this patient?" All doctors do this more or less automatically The more you do it consciously and thoughtfully, the better the patient's chances of getting the greatest possible help. It need not require more time, but rather a heightened awareness of the *whys* as well as the *whats* of the patient's discourse and behavior.

It helps to ask yourself *specific questions* With regard to your relationship with the patient, these might include· What influences other than his "chief complaint" led him to consult me at this particular time? Why did he pick me? What does he expect from a doctor? What do I expect of him? Of myself in this situation? Assuming that he wants to make a good impression on me, what does his present behavior tell me about what he expects of himself and of others? What things about him do I like or dislike?

One might characterize such inquiry as an attempt to become unusually aware of this human being's "style" in his dealings with you, and of your reactions to it. Such awareness helps you to plan a treatment program which the patient will accept. Equally important, it is an appropriate starting point in your assessment of the psychic factors in his illness. The rough spots in his relationship with you are usually prototypes of problems he has faced for many years in his relationships with others.

Allow personal material to emerge early in the initial interview. Where appropriate, phrase some questions vaguely: "Do you have any explanation for this illness? Tell me about your work. How are things at home?" etc If an answer seems irrelevant, postpone any interruption long enough to estimate why the answer is important to the patient

Ask supplementary specific questions, pertinent to psychic symptomatology, as a part of the initial interview. The patient's handling of the question "Have you ever had a nervous breakdown?" often yields information about his understanding of, and attitude towards, psychic illness, insanity, psychiatrists, etc. "What sorts of bodily symptoms do you get when something upsets you?" will elicit information about his awareness of emotions, insight, and probable reaction to any subsequent psychosomatic formulations of symptoms. It may also reveal a common point of departure for subsequent discussions

The early timing of such inquiry is important To postpone it for a "second round," perhaps after laboratory results are available, may raise unnecessary obstacles. The patient may correctly or incorrectly paraphrase the physician's actions thus "I can't find anything seriously wrong—it may all be in your mind I don't talk about these things with most of my patients—i e , those with 'legitimate' disease " If the patient has set the pace of the early part of the initial interview and relevant

psychic material has clearly emerged, then it is the physician who restores balance, conservatism, and the assurance that no possible treatment will be overlooked, by obtaining a complete medical history and appropriate tests.

Continuing Treatment. The most appropriate plan of psychotherapy may in rare cases be a tacit understanding that psychic considerations are totally irrelevant to the present problem. This may be true either of patients with little intelligence or capacity for insight, or of patients who probably are painfully aware of severe problems in adjustment, or of deviations from social norms, but would really prefer to have the physician "mind his own *business*"

At the other extreme, a few hypertensive patients can most appropriately be treated by a psychiatrist, if one is available Practically, these are usually patients who will accept the idea, are intelligent, can afford it, and are aware of relatively severe psychic symptoms. The psychiatrist can be of help in many more cases in the role of consultant. Psychiatric referral should convey the message, "We need an expert opinion on this aspect of the problem," rather than "What you need for *your* trouble is a psychiatrist." Whenever possible, you and the psychiatrist should be familiar with each other's individual interests, methods, and capabilities An ideal arrangement, when geography permits, is for the psychiatrist to come to your office and interview the patient in your presence.

Most hypertensive patients fall between the two extremes just discussed When your preliminary evaluation is complete, define the problem for the patient and explain his hypertension to him in terms which you think he can accept Propose further discussions of some of his problems as a frequently successful means of reducing symptoms Encourage him to look at the life settings in which symptoms arise. Make it clear that the symptoms are not imaginary, that they are not caused by high blood pressure per se, and that when you say "troubles can give rise to such symptoms," you are simply saying that he is human The patient may quickly see relationships between symptoms and problems but prefer not to admit this to you A patient often views psychosomatic interpretations as insults, not only to himself and his family, but to physicians consulted in the past who have not raised such issues.

There is a formidable list of medication that might seem indicated for headache, fatigue, backache, flatulence, constipation, nervousness, and insomnia. The patient should at least be exposed to the idea that there may be better ways to attack symptoms. His reaction to this idea is one index of what one can hope to accomplish by "psychotherapy" prescribed as such. One tries to hold symptomatic medication to a minimum, thus registering a vote of confidence in the patient's ability to change, without causing useless distress or expecting more of the patient than he can accomplish. If antihypertensive drugs are not urgently indicated, there are good reasons, to be given later, for not using them immediately.

There can be no adequate attempt in this discussion to convey what one "does" with personal material as it emerges. The physician's major role here is to ask for information and to define areas of conflict. Specific advice about the patient's conduct in a difficult situation usually does more harm than good.

Skill in this area improves with experience and training. Most physicians are aware of a lack of both The physician may thus be at an unnecessary disadvantage when the patient says directly or by innuendo. "You aren't helping me enough" In feeling defensive about the justice of the accusation, the physician may miss the point, namely that the patient thinks he has limitless healing powers, but is withholding them because of the patient's unworthiness The physician's limitations can be used as an impetus towards an important goal—that the doctor-patient relationship, which so frequently recapitulates that of parent and child, becomes one between two adults "side by side" The physician who is jealous of his power will only reinforce the patient's habits of suspicious, hostile, dependent compliance

Within a few weeks or months, symptoms may have diminished greatly, but the hypertension is usually unaltered The patient feels that he is beginning to repeat himself. The physician has a better understanding of the patient's problems but does not see what more he can do to help the patient meet them. Th

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3

Pathology in systemic hypertension

SIMON KOLETSKY

The principal pathologic lesions in patients with long-standing hypertension occur in the heart, the peripheral vascular bed, the kidneys, and the brain

The *heart* is enlarged, mainly because of hypertrophy of the left ventricle The organ is increased in weight, usually to levels of between 400 to 600 Gm, but even the latter figure can be exceeded There is an increase in width of the left ventricular wall, which usually measures from 2 0 to 3 0 cm in thickness, and this is associated with enlargement and prominence of the trabeculae and papillary muscles (Fig 12-1) Initially, the cardiac hypertrophy involves principally the outflow tract, from apex to aortic orifice, and this often appears considerably lengthened Two forms of hypertrophy are described, concentric and eccentric In the former, the walls are thick and the chambers reduced in size, while in the latter, increased weight is associated with enlarged chambers

The increase in cardiac weight is probably due solely to *increase in size or thickness of the individual muscle fibers* The sarcoplasm is increased in amount, and the nuclei become enlarged and show blunting of their ends Apparently the fibers do not tend to become uniformly enlarged. No abnormality other than increase in size of the fibers is commonly seen, although there may be such retrogressive change as vacuolization or fatty degeneration of the muscle cells Interstitial fibrosis in the absence of significant narrowing of the coronary arteries is not common

The left ventricular hypertrophy in hypertension is attributed to the increased resistance offered by the peripheral vascular bed to discharge of blood from the chamber. According to the present concept, *the hypertrophy is preceded by dilatation of the chamber* resulting from retention of blood because of the initial inadequate output. Roberts and Wearn thought that the limits of compensation by hypertrophy are probably related to blood supply. While the number of capillaries remains the same during hypertrophy, they are spaced farther apart as the muscle fibers enlarge, and thus have to supply a larger mass of muscle from a greater distance. Both factors hamper adequate exchange of oxygen and metabolic



Fig. 12-1. Cardiac hypertrophy in a patient with hypertensive heart disease The heart weighed 600 Gm Note thick left ventricular wall, together with prominence of papillary muscles and trabeculae.

patient can be warned in advance that this often happens. The warning helps the patient to maintain a realistic view of the physician as an experienced but still limited human being.

In the over-all plan of treatment, this is an appropriate time to initiate antihypertensive drugs, if they seem indicated, the patient having been told previously that they may be necessary. By this time, much helpful "baseline" information is available. In addition, by delaying antihypertensive drugs, the physician indicates more clearly than he can with words the chronic nature of the disease and his conviction that hypertension in itself is not a medical emergency. When started, the medication can represent to the patient a long-term means of keeping the blood pressure within safe limits. He deserves to know that some situations and reactions can cause his blood pressure to be higher or lower, but "specific" medication prevents the useless hardship of regarding every crisis as a threat to life. He gains courage in his efforts to abandon old patterns of resentful dependency. At the same time, he is forced to avoid the temptation to take unfair advantage of others by asserting his disease, rather than himself, when conflicts arise.

Following the periods of initial enthusiasm and subsequent disenchantment, physician and patient can settle into a supporting, hopeful, conservative relationship. Presumably, any psychic benefit to the hypertension is independent of the declared goals of therapy. The door is open for continuing discussion of psychic problems. The physician is fully justified in charging for the time spent in such discussions. The patient must understand that the goals of greater self-esteem and loss of useless anxieties are, by themselves, realistic and worthy.

the marked predilection of the kidneys of hypertensive patients for the vascular lesions. In contrast to the belief that hypertension causes the vascular disease, it has been suggested that *renal arteriolar disease is the primary lesion and serves to initiate the hypertension*

The vascular lesions of *chronic hypertension* have been described in detail by Moritz and Oldt. The most common change is intimal hyalinization, consisting of subendothelial deposit of homogeneous acidophilic material, which appears to represent an infiltration or expansion of the ground substance between the media and the endothelium This is commonly associated with either fatty or hydropic degeneration The hyalin is disposed as a circumscribed subendothelial plaque, or forms a subendothelial collar of uniform thickness, or can be annular and of irregular thickness It often involves the internal elastic membrane and may produce swelling, disruption, or obliteration of the lamellae Marked hyaline change may result in considerable narrowing of the lumen of the vessel

Another frequent lesion is endothelial hyperplasia, especially in vessels over 50 μ in diameter This change can also produce substantial reduction of the vessel lumen. The hyperplastic endothelial cells tend to become spindle-shaped and resemble connective tissue cells. Commonly, the proliferative change is associated with increase in elastic fibers between the newly formed endothelial cells. There is usually formation of more or less concentric elastic lamellae, giving the appearance of *splitting or reduplication of fibers.*

The medial coat shows two types of change One consists of hypertrophy and is manifested by increase in the number or size of smooth muscle cells and increased thickness of the layer, and the other is represented by a relative increase in the amount of intercellular collagen throughout the media. The latter is not associated with fibrocytic proliferation, is more pronounced in the inner than in the outer half of the media, and in some instances results in atrophy rather than in hypertrophy of the smooth muscle cells.

In so-called *malignant hypertension*, acute necrotizing lesions are superimposed on the *chronic* arteriolar disease. This change is most common in the kidneys (Fig 12-2B), especially in the afferent arterioles of glomeruli, but



Fig 12-2. A Granular kidney (nephrc … with long-standing hypertension. The outer surface is uniformly nodular. B Kidney of patient with malignant hypertension and renal failure Note vessels showing proliferative endarteritis, A; hyalinization of wall, B; and fibrinoid necrosis, C; also partly hyalinized glomerulus, D. Hematoxylin and eosin ×225.

products, and the result is impairment of muscle metabolism.

In instances of supervening cachexia, such as occur with disseminated carcinoma, chronic hypertension may not be associated with cardiac hypertrophy at the time of death In this circumstance, the heart has presumably undergone atrophy due to the cachexia, and this may be indicated by tortuosity of the coronary arteries.

Coronary arteriosclerosis tends to be more frequent and severe among patients with hypertensive heart disease than among nonhypertensive persons (Bell and Clawson). Apparently, hypertension favors the development of coronary sclerosis. About half the patients with acute coronary thrombosis and myocardial infarction have had previous hypertension. By its effect on cardiac nutrition, progressive coronary disease may limit compensatory reserve of the heart in hypertension and hence lead to myocardial failure. However, the relation of degree of cardiac enlargement to coronary disease is not entirely clear. Marked hypertrophy is observed both in hypertensive patients with significant narrowing or occlusion of the coronary vessels and in hypertensive patients with minimal coronary disease.

Along the same line, *no* clear interrelationship has been established between hypertension and arteriosclerosis of the large vessels For example, extreme arteriosclerosis of the aorta is observed in individuals who did not have elevated pressure, and conversely individuals with long-standing hypertension frequently show large-vessel disease not significantly more advanced than that observed in the corresponding age group without hypertension. However, *dissecting aneurysm of the aorta* is clearly related to hypertension from the pathogenetic standpoint.

No significant lesions of endocardium or pericardium occur in uncomplicated hypertensive vascular disease. Mural thrombi of ventricular or atrial endocardium are usually secondary to infarction from occlusive coronary disease. In cardiac arrhythmias, especially atrial fibrillation, or in decompensation, stasis thrombi occasionally develop in the auricular appendages and may serve as the source of emboli to brain, kidneys, spleen, and extremities.

When *cardiac insufficiency* supervenes, especially with repeated attacks of decompensation, the hypertrophy of the left ventricle is accompanied by dilatation and enlargement of the chambers, a corresponding decrease in the thickness of the wall, and flattening of the columnae carneae and papillary muscles. Also, the other chambers of the heart become hypertrophied and usually dilated. *Right ventricular hypertrophy* is a consequence of passive congestion of the lungs (due to long-lasting left heart failure). The enlargement of the chambers may be sufficiently marked to cause relative insufficiency of one or both AV orifices

Patients with *congestive heart failure* show passive hyperemia of the abdominal viscera. This varies in degree according to the duration and severity of failure For example, the *liver* may have prominent dark red central-zone markings, discrete or with lobular confluence, accumulation of fat giving the characteristic reddish-yellow *nutmeg liver,* or even cardiac cirrhosis Extravasation of fluid, usually of clear serous type, in the pleural and pericardial cavities, i.e , hydrothorax and ascites, and edema of the lower extremities, are also consequences of heart failure.

In hypertension, there are widespread lesions of the small arteries and arterioles These are most pronounced and frequent *in the kidneys* but are also found in the pancreas, gastrointestinal tract, adrenal gland, liver, brain, choroid, and skeletal muscles. Vascular changes occur in the spleen but are difficult to evaluate since spontaneous lesions in this organ are common in nonhypertensive individuals. The lesions in skeletal muscle are sometimes sufficiently well developed so that biopsy indicates the presence of vascular disease clinically (Foa et al).

Some investigators have regarded the vascular alterations associated with hypertension as similar to those occurring in arterioles on a physiologic basis with advancing age; i e., intimal hyalinization is the arteriolar counterpart of simple arteriosclerosis Such lesions are then believed to be hastened and accentuated by the vascular strain resulting from elevated blood pressure However, it cannot be stated with certainty from available evidence that hypertension actually plays a major role in the production of diffuse vascular disease In particular, it is difficult to explain on this basis

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In so-called *malignant hypertension*, acute necrotizing lesions are superimposed on the chronic arteriolar disease. This change is most common in the kidneys (Fig. 12-2B), especially in the afferent arterioles of glomeruli, but



Fig 12-2. A Granular kidney (nephr[illegible] [illegible] with long-standing hypertension. The outer surface is uniformly nodular. B. Kidney of patient with malignant hypertension and renal failure. Note vessels showing proliferative endarteritis, A; hyalinization of wall, B; and fibrinoid necrosis, C, also partly hyalinized glomerulus, D. Hematoxylin and eosin ×225.

may occur elsewhere, as in the gastrointestinal tract, adrenal glands, pancreas, liver, and brain. The necrosis consists of a smudgy, densely acidophilic accumulation of fibrinoid material, either homogeneous or granular, more or less obliterating the underlying structure, which shows partial or complete loss of nuclei. The fibrinoid substance frequently shows interspersed fatty vacuoles or extravasated red blood cells. Aneurysm, thrombosis, and hemorrhage may accompany the lesion As a rule an exudative component is either slight or absent

The necrotizing process is variable in extent. In the small arterioles, it tends to occupy the entire wall of the vessel, with substantial reduction of the lumen, but it may be patchy and involve only part of the wall Sometimes only the intimal layer shows the change and the lesion appears to be essentially subendothelial in location. However, the internal elastica is involved and reveals disruption, dispersion, or obliteration of fibers As is the case with the chronic arteriolar changes, the necrotizing process is commonly segmental in distribution along a given vessel.

In many instances of long-standing hypertension, the lesions of the kidneys constitute a striking feature of the pathologic picture (Fig 12-2A) This refers to the characteristic granular kidneys of hypertension, which comprise the picture designated as arteriolar nephrosclerosis. The organs are firm and slightly reduced in size, although occasionally they are substantially smaller than usual, and the capsule strips with increased difficulty. The outer surface is finely and uniformly granular, and small nodules of parenchyma, about 1 or 2 mm in size, project slightly above the reddish-gray network of retracted fibrous connective tissue. The organ cuts with increased resistance, and the cross section shows a narrowed cortex with indistinct striate pattern, medullary pyramids which are reduced in size, and thickening of the visible branches of the renal arteries.

The *nephrosclerosis*, which usually accompanies chronic hypertension, may vary from well developed to slight. On occasion, however, the kidneys of hypertensive patients appear grossly normal. While microscopically such organs as a rule show arteriolar sclerosis without parenchymal atrophy and fibrosis, there are instances where the kidneys show vascular disease which is apparently minimal and difficult to appraise as more significant than that present in nonhypertensive individuals. Observations of this kind have been cited as not supporting the concept of the renal origin of essential hypertension. A related item is the failure to find significant arteriolar sclerosis consistently in renal biopsies from patients in the early stage of hypertensive disease (Castleman and Smithwick).

The *renal lesion* consists essentially of an ischemic atrophy of parenchyma which is the result of arteriolar sclerosis Microscopically, there are glomerular lesions which range from thickening and wrinkling of the basement membrane to adhesions between tufts, hyalinization of tufts, and partial or complete conversion to fibrous whorls The tubules show secondary atrophy, and this is associated with interstitial fibrosis and lymphocytic exudate Nephrons with minimal involvement may reveal compensatory hypertrophy of tubules, but eventually these show degenerative change of granular, fatty, or hyaline-droplet type. The lesions of the small arteries and arterioles, as described above, are frequently pronounced. In malignant hypertension, the superimposed fibrinoid necrosis involves especially the vasa efferentia and may also involve the glomerular tufts As a consequence, there is extravasation of blood, and collections of erythrocytes within the tubules may be sufficiently extensive to produce grossly visible *petechiae*, best observed in the outer surface of the kidney after stripping the capsule Also the glomeruli frequently show proliferative lesions of the epithelium, adhesions between tufts and cellular exudate, producing a picture similar to that seen in acute glomerulonephritis. Especially marked in the malignant phase is endothelial proliferation of vessels, which is associated with elastic fiber reduplication and severe reduction of vessel lumens

In the *brain*, the most common pathologic lesion is *hemorrhage*, which often results in hemiplegia Hemorrhage is usually due to rupture of one or more of the small branches of the lenticulostriate arteries Since the latter arise at right angles from the middle cerebral artery, they may be subject to higher intravascular pressure than the usual dichotomous branches Moreover, the vessels are usually arteriosclerotic, and this may reduce their re-

sistance to internal pressure and lead to rupture Perhaps rupture of intramural miliary aneurysms of diseased arterioles may be a source of bleeding *It is believed by some that hemorrhage takes place from vessels situated in tissue previously devitalized by vasospasm, thrombosis, or embolism* (Globus). In malignant hypertension, there are often small foci of hemorrhage, necrosis, and edema associated with arteriolar necrosis.

The hemorrhage is usually well-defined and varies in size from a minute focus to a mass occupying most of the hemisphere. As the blood extravasates, it destroys nerve substance and compresses the surrounding structure *Cerebral edema* results, and the increase in intracranial pressure may cause death through herniation of the brain and compression of the brain stem. The hemorrhage may rupture into the subarachnoid space or into the ventricles. The blood clots rapidly, and the cross section is dark red and relatively dry The larger hemorrhages occur in the basal ganglia, thalamus, white matter of cerebral hemispheres, pons, and cerebellum

Microscopically, the region of recent hemorrhage shows infiltration of mononuclear cells and polymorphs. Scavenger cells appear and phagocytize the debris of tissue and myelin. The breakdown of blood furnishes both hemosiderin and hemotoidin, and these pigments are taken up by phagocytic cells Reactive gliosis and fibrosis are present, and the hemorrhage becomes cicatrized if small, or encysted if large The latter is typical of an area of remote encephalomalacia. The cyst is filled with thin fluid, usually brown or yellow in color, and the cyst wall is of similar but usually deeper color because of the presence of free pigment between cells and fibers. The cavity of the cyst may be traversed by a delicate weblike net of connective tissue fibers When recent or remote cerebral infarcts are observed in patients with hypertension, they usually are the result of thrombosis of sclerotic cerebral arteries or embolism from the heart. Recent infarction is usually *not associated* with significant gross hemorrhage. Healed *infarcts* are difficult to distinguish from foci of remote hemorrhage with cyst formation

4

Biochemical aspects of hypertension

HENRY A. SCHROEDER

All biologic phenomena can be eventually defined in terms of physics and chemistry. Although few such phenomena are comprehensible in these terms, a review of what is known of the abnormal biochemical changes in arterial hypertension may be rewarding, for intelligent therapy is directed towards reversing these changes.

The changes resulting in chronic generalized vasospasm leading to increased blood pressure are obviously of cellular origin and are probably a manifestation of altered cellular metabolism. The tissues involved are the vasomotor nerves, adrenal glands, kidneys, and smooth muscles of arterial and arteriolar walls After each area has been examined separately, their interactions may then be considered

ARTERIAL MUSCLE

There is no doubt that the smooth muscle fibers of the arterioles and small arteries are constricted in hypertension; the evidence for this assumption is indirect but overwhelming There is some evidence that smooth muscle of all arteries is constricted (Schroeder, 1953) The degree of constriction which causes profound increases in peripheral resistance may be very small, for *resistance varies as the fourth power of the radius of the vessel's lumen*. Indirectly, it is known or surmised that vessels to all organs and tissues are constricted approximately equally throughout the body, with one exception: arteries and arterioles of the kidneys are somewhat *more* constricted than the others (Goldring and Chasis, 1944).

Three mechanisms have been proposed to account for this fairly uniform vasospasm: (1) the sympathetic vasoconstrictor nerves are hyperactive; (2) there is a vasoconstrictor substance in blood which acts directly on smooth muscle, (3) smooth muscle becomes "sensitized" to normally acting sympathetic nerves or constrictor substances. As will be discussed, any two or all of these mechanisms can be active in human cases

The *reactivity of muscle*, probably including smooth muscle, can be affected by *alterations in ionic relationships*. Calcium, magnesium, sodium, potassium, hydrogen, and hydroxide ion concentrations affect muscular irritability according to the following schematic ratio in extracellular fluid

$$\frac{[Na^+ + K^+ + OH^-]}{[Ca^{++} + Mg^{++} + H^+]}$$

An increased concentration in the numerator increases irritability, an increase in the denominator decreases it This ratio appears to hold for vascular smooth muscle, in so far as is known *Thus, sodium, potassium, and alkalosis enhance vascular reactivity when increased in extracellular fluids, while magnesium, calcium, and acidosis decrease reactivity* (Sollmann, 1948) The situation is not so simple as this, however, for what is *inside* the cell membrane is obviously the determining factor, and this factor is governed by the permeability of the cell membrane to specific ions and its ability to transfer or reject ions (the "pump") Therefore, cellular reactivity probably depends upon a potential governed in part by the gradient between what is inside and what is outside in terms of a specific ion

Cellular permeability is affected presumably by both hydrogen ion concentration and total osmolarity, furthermore, displacement of *one ion* by another (sodium for potassium, for example) appears to occur within the cell under certain clinical conditions. Therefore, the interrelationships of the bulk cations in affecting muscular irritability can be complex when considered in the whole body.

A further restriction of this ratio to the *potassium gradient* alone has been found in work on *nerve*, skeletal muscle, and smooth muscle (Bohr, Brodie, and Cheu, 1958) When K_I is the intracellular and K_E the extracellular concentration, and C is a constant, then

$$\text{Log}\,\frac{K_I}{K_E}\times C = \text{resting potential}$$
$$= \textit{threshold for response}$$
$$= \frac{1}{\textit{responsiveness}}$$

By this formula, sodium, magnesium, calcium, and hydrogen ion concentrations are not involved. They do, however, exert effects singly on reactivity and must be taken into consideration in any uniform theory, even if their effects on the gradient of intracellular-extracellular potassium turn out to be indirect.

Although permeability of cells to cations is altered by overhydration, dehydration, acidosis, or alkalosis, for purposes of this discussion consideration will be confined to *permeability to* sodium, potassium, and magnesium This function appears to be under partial control of some adrenal cortical hormones. *Desoxycorticosterone acetate* and *aldosterone* have the property of causing cells to gain sodium and lose potassium and possibly magnesium (Hajdu, 1953)

One interesting and fundamental observation has demonstrated that vascular smooth muscle of hypertensive rats and patients actually contains more sodium than normal muscle, and is therefore possibly edematous In rats, hypertension caused by either *renal* ischemia or the administration of *desoxycorticosterone* was accompanied by aortic smooth muscle containing more *sodium* and potassium and *less* magnesium than that of *control animals* (Tobian and Binion, 1954). The *renal* arteries of hypertensive patients showed more sodium and water, with *normal* potassium and magnesium concentrations (Tobian and Binion, 1952). This finding has led to the postulate that *swelling of the wall* (rather than *active vasoconstriction*) *accounts* for the increased resistance in the peripheral vascular bed leading to hypertension It does not rule out, however, the probability that such vessels are hyperreactive

In hypertensive patients, examination of the blood which bathes vascular smooth muscle shows the following: slightly *increased sodium* concentration (with considerable overlap), slightly decreased *magnesium concentration (with considerable* overlap), normal potassium concentration (Albert et al., 1958). It is possible that these tendencies, in themselves not diagnostic, are a reflection of a slight overproduction of mineralocorticoids by the adrenal cortex, for excessive production causes changes in the same directions.

ADRENAL CORTEX

Among the several steroids secreted by the adrenal cortex, one is primarily concerned with electrolyte balance and thus, indirectly, with vascular reactivity: *aldosterone*. Although many attempts have been made to *implicate* the adrenal cortex in hypertension, *there is no* clear-cut evidence that this organ initiates or *maintains* hypertension save in one condition: *when* the cortex itself is hyperplastic or contains an adenoma which secretes aldosterone. Then, *and only then*, is there proof of cause and *effect*, for removal of the adenoma usually causes regression of the disease (Conn, 1955)

In spite of the lack of evidence, *bilateral adrenalectomies* have been performed *for* hypertension with variable results. *In* the *absence of the* adrenal glands, the body finds *it difficult* or impossible to maintain vascular *tone and* reactivity; untreated Addison's disease *and* severe hypertension cannot exist together Therefore, the fact that blood *pressure may* fall after adrenalectomy *is in* no way indicative of prior hyperactivity *of* the gland, for normal blood pressure likewise will fall after adrenalectomy

Patients with certain *types* of *cortical adenomas* excrete excessive amounts of aldosterone in their *urine* and show sodium retention, urinary *loss of* potassium, and hypertension (Conn, 1955). *These* findings usually revert to *normal* when the adenoma is removed, although the *hypertension* may not *entirely*

regress. However, most hypertensive patients excrete a slight excess of urinary aldosterone (Genest et al., 1956), and some show the plasma electrolyte changes enumerated above. Therefore, the effects of steroids on electrolytes and on vascular reactivity should be examined in order to ascertain what possible primary or secondary etiological actions they might have.

Adrenal Cortical and Electrolyte Influences on Vascular Reactivity. There is no doubt that salt and steroids can affect general vascular reactivity (Goldman and Schroeder, 1948). *Desoxycorticosterone* (*DOC*) has been the most widely studied; it and sodium chloride produce experimental (rat) hypertension (Braun-Menéndez, 1951) and a syndrome similar to toxemia of pregnancy (Masson et al., 1953). Although DOC alone will not cause hypertension in rats, salt alone in large amounts will (Sapirstein et al, 1950). In man, the vascular response to graded doses of epinephrine and norepinephrine is enhanced by DOC and depressed by severe restriction of dietary salt (Raab et al, 1952), although these findings were not wholly confirmed by Dahl (1957) Hypertension has sometimes accompanied the chronic administration of adrenocorticotropic hormone (ACTH), cortisone, and hydrocortisone, and patients with Addison's disease frequently become hypertensive when treated with salt and DOC (Perera et al, 1944)

The mechanism of this increased irritability has not been exactly elucidated Probably it involves intracellular alterations in the four cations concerned in smooth muscular reactivity; one could make a reasonable assumption that the potassium-sodium ratio in the cell was lowered or the magnesium-calcium ratio was changed, or both. This basic point deserves careful study of the four ions and the effects of steroid hormones upon their intracellular-extracellular balances.

When these various findings are considered together, it appears that salt and adrenal cortical steroids somehow cause a change in arterial smooth muscle. This change has been characterized by hyperirritability to the injection of the vasoactive agents epinephrine and norepinephrine Depletion of salt reduces irritability. Therefore, *a present concept of some forms of hypertension involves alteration in sodium, potassium, and possibly magnesium ratios within the smooth muscle cell, making it more sensitive to normally acting vasospastic influences* This alteration results from remote influences involving intake, excretion, and steroids.

Therapeutic Implications. Measures aimed at depletion of body sodium in the hope that this cellular alteration may be reversed involve severe restriction of dietary salt (Kempner, 1948), promotion of urinary excretion of sodium by electrolyte diuretics (Taggart, 1958), and (experimentally) the use of antiadrenal compounds (Stafford et al, 1953, Schroeder, 1953; Sturtevant, 1957). All these measures are moderately effective in some patients. That this cellular electrolytic alteration is not the *sole* cause of *all* hypertension (although it may be the primary cause in a small percentage) is suggested by the failure of these methods completely to reverse the vasospastic state in all patients

State of Kidneys with Respect to Salt. Hypertensive kidneys excrete more salt in response to a salt load (intravenous hypertonic saline solution) than do normal kidneys (Farnsworth and Barker, 1946; Green et al, 1952) This abnormal response is the one renal metabolic defect which seems to be consistent They also excrete more sodium and chloride during a resting period, provided the hypertension is not severe Even patients with mild hypertension and normal renal plasma flow excrete more urinary sodium, potassium, and chloride than do normotensive subjects (Cottier et al, 1958) Therefore, *the hypertensive kidney is a salt-losing kidney.* Obviously such chronic salt loss would be difficult to measure and would in time result in a state of severe hyponatremia unless the lost salt were replaced by diet and attempts made by the body to conserve it

Because of this defect, it may justly be theorized that regulatory forces probably come into play in order to maintain body sodium These involve increased formation of aldosterone in order to conserve urinary salt, and increased salt intake perhaps a result of salt hunger However, the actual losses needed to call out conserving mechanisms, when considered in the long term, may be small, for there is only a bit more than 120 Gm exchangeable salt in the adult body, and only about 20 Gm in the blood

Therefore, in hypertension, there are found the following alterations with respect to electrolytes and their hormonal governors salt-losing kidneys, slightly increased excretion and presumably formation of aldosterone, possible ingestion of more than normal amounts of salt, and hyperirritability of vascular smooth muscle, probably resulting from sodium and potassium imbalances within the cells as a result of excess aldosterone production One may well ask which comes first? The answer is not known, but the clinical indications are that *in some, probably few, cases the process is initiated by excessive production of aldosterone from an adenoma, while in most cases the renal defect initiates the adrenal mechanism as a compensatory phenomenon*

THE RENAL BIOCHEMICAL ABNORMALITY

Little is known of the exact biochemical abnormality in the kidneys of hypertensive persons Until the hypertensive process has damaged the kidney by causing renal vascular disease, the urine may appear normal, renal function may be normal by all the usual gross tests, and no abnormality of blood suggestive of renal disease may be found There are, however, several hidden alterations which can be detected by special procedures. There is usually a little more urinary sodium chloride and water than in normal persons, the pH tends to be a bit more acid, and the ratio of ammonia to titratable acid is reduced (Perry and Schroeder) The renal plasma flow is reduced in all cases but the mildest, when it may be normal at rest, glomerular filtration rate is usually increased in relation to total plasma flow, and the calculated result suggests constriction of the efferent arterioles (Goldring and Chasis, 1944) Oxygen consumption by the kidney is usually found, by calculation, to be reduced (Schroeder, 1953, Huckabee, 1958) Primary amines in blood are elevated (Stock and Schroeder, 1950; Olsen and Schroeder, 1950a)

A little more is known of the changes in experimental hypertension Oxygen tension of the renal cortex is reduced (Olsen and Schroeder, 1950b) Oxygen consumption by the kidney may be reduced (Olsen, 1951) The cortex is acid (Olsen and Schroeder, 1950b) When kidneys are removed, they show enzymatic changes: reduced amino acid oxidation, reduced deamination of amines by monamine oxidase, reduced transamination (Olsen, 1951), reduced dehydrogenation of succinate and oxidation of cytochrome (Raska, 1943) Thus, there is a general depression of oxidative enzymes, which may be specific or may be the result of destruction of renal tissue by the procedure. Naturally, one wonders how these alterations can raise blood pressure, if they do The exact pathways are unclear, although there are a number of attractive hypotheses to explain them.

To account for the increase in primary amines (most of which are vasoactive) there is the theory of Holtz (1939), which deals with two types of enzymes, certain amino acid decarboxylases and monamine oxidase.

Decarboxylases are known for tyrosine, dihydroxyphenylalanine (DOPA), tryptophan, 5-hydroxytryptophan, leucine, and histidine. These amino acids, when they lose their carboxyl groups, form the vasoactive amines tyramine, dihydroxyphenylethylamine, tryptamine, serotonin, isoamylamine, and histamine, which are then deaminated to their unstable aldehyde degradation products by monamine oxidase and, in the special case of histamine, by histaminase or diamine oxidase Deamination by monamine oxidase requires oxygen, and the enzyme is especially sensitive to oxygen lack, its activity being in direct relationship to oxygen tension (Kohn, 1937) Decarboxylases are anaerobic, requiring no oxygen for activity

It is probable that some urinary ammonia comes from amino acids other than glutamine, which has been shown to contribute about two-thirds of the total ammonia excreted There is a divergence of opinion on this matter, but several amino acids are capable of contributing ammonia (Meister, 1956), partly through the pathway described. One can then logically predict some of the fundamental changes which would take place if renal oxygen tension were reduced enough partially to inhibit renal monamine oxidase. Decarboxylation would proceed anaerobically as usual Primary amines resulting therefrom would escape deamination by the kidney and would enter the general circulation Those that escaped deamination in the lungs (where there is considerable monamine oxidase) would act on blood vessels in the periphery, including the kidney, deamination would be shifted from

kidney to pulmonary and systemic blood vessels and liver. In the urine there would be less ammonia and a little more sodium, with a tendency for the urine to be on the acid side. The cortex of the kidney would be acid. Primary amines would be found in arterial blood in increased amounts. In other words, *reduction in renal oxygen tension would cause all the minor abnormalities which are actually found* (Schroeder, 1957).

Would these metabolic changes raise blood pressure? Probably not. Aside from the amine of DOPA, the others are relatively weak pressor substances, and relatively large amounts would be necessary to cause chronic hypertension unless monamine oxidase were also depleted from the body (Schroeder and Olsen, 1950b). They would also have been detected in large amounts before this time. One can accept the fact that renal oxygen consumption and oxygen tension are reduced in most cases of hypertension, but this alone cannot be implicated as a cause. One must look for more powerful pressor substances

Two converging lines of investigation, conducted for the past 20 years, proved to be rewarding. One has involved the isolation of a pressor substance from arterial blood of hypertensive patients (Schroeder and Stock, 1942). This substance, probably a polypeptide, constricts vascular smooth muscle which has been blocked by sympatholytic agents, i e., it is a direct muscle stimulant (Schroeder et al, 1955). It has been named *pherentasin* (Schroeder and Olsen, 1950). It can be obtained from extracts of arterial blood of moderately severe and severe cases of hypertension, but little or none is found in mild cases Restoration of normotension by chemotherapy results in its disappearance.

The other has involved *angiotensin*, a polypeptide resulting from the enzymatic action of renin on an alpha 2 globulin in blood (Braun-Menéndez et al., 1940, Page and Helmer, 1940).[1]

Renin is a proteolytic enzyme in kidney which is released into the renal venous blood under conditions of acute reduction of renal blood flow. Upon release, it reacts with its substrate, providing a decapeptide, *angiotensin I* (Skeggs et al, 1954). A peptidase in blood, called the converting enzyme, removes two of the amino acids, resulting in the very active vasoconstrictor octapeptide, *angiotensin II* (Lentz et al., 1956). Both these peptides have been synthesized (Bumpus, Schwarz, and Page, 1957). A substance with the activity of angiotensin has been obtained from hypertensive blood by alcoholic precipitation (Skeggs et al, 1952).[2]

Unfortunately for the renin hypothesis, no renin has been found in renal venous blood in chronic hypertension (Taquini and Fasciolo, 1949, Braun-Menéndez et al., 1946; Quimby et al., 1945) Although repeatedly searched for, renin release ceases after a few days or weeks of chronic renal ischemia Therefore, *it is generally agreed that while renin may be the effector substance for acute vasospastic states such as congestive heart failure, acute nephritis, toxemia of pregnancy, etc.* (Dexter and Haynes, 1944), *it can scarcely be involved in chronic vasospastic states because it is not found in them.* The discrepancy between finding an angiotensin-like substance presumed to be the product of the reaction of renin, and not finding renin, has not been resolved.

Be that as it may, extracts of human hypertensive blood do contain a vasoactive substance of peptide nature, whether this substance is called pherentasin or angiotensin and whether it comes from the kidney or elsewhere The two substances, pherentasin obtained from human blood and angiotensin obtained from animal kidney and animal globulin, are remarkably similar in most, but not all, of their reactions (Schroeder, 1957). If pherentasin is actually human angiotensin, the differences may be ascribed to different amino acids in the species-specific globulin (Braun-Menéndez and Paladini, 1958). Again this point has not been resolved

At any rate, it is fairly safe to assume that part of the chronic vasospasm found in hypertensive states is caused by a peptide in blood, released probably by proteolysis, but with its

[illegible] to the material
by [illegible]
by [illegible]
term [illegible]
Buntz, 1958).

[2] It is probable that the material procured from blood is the same substance called pherentasin in this discussion, for methods of extraction and concentration are similar. It has not been chemically identified as angiotensin

actual source unknown. *All the indirect evidence, however, points to the kidney as the source.*

The nature of this peptide is not known. By analogy with angiotensin, which it resembles in its direct vascular action and in reactions designed to inactivate it, this peptide probably contains eight amino acids, of which aspartic acid and arginine are at one end and phenylalanine at the other (Elliott and Peart, 1956; Skeggs et al, 1956, Rittel et al, 1957) There is a distinct possibility, however, that many hypertensins may result from proteolysis Until the substance in blood is purified and its amino acid content is characterized exactly, one can learn little more about it and from whence it comes.

NERVES

An increase in the "tone" or reactivity of sympathetic vasoconstrictor nerves could easily result in intermittent hypertension and its characteristic renal hemodynamic profile Opinions and experiments differ on whether or not sympathetic nerves discharge more easily, i e, have a hair trigger response, in hypertension than in normotension Data convincing enough must be indirect, experiment is now most difficult, if not impossible, in human subjects *In the experimental animal, but not in the human being, there is indirect evidence that in the later stages of renal hypertension, the sympathetic nerves are more active and play an increasingly important role in the chronic vasospasm, while in the early stages the role of the kidneys is predominant* (Ogden, 1947)

In human beings, the indirect evidence for increased sympathetic nervous activity is as follows The blood pressure may be labile and widely variable, especially in cases with no demonstrable renal involvement (Schroeder, 1957). Traube-Hering and respiratory variations are often marked (Janeway, 1904; Schroeder and Menhard, 1956) The pressor or vasospastic effects of central vasomotor stimuli, from inhalation of carbon dioxide [illegible]

[illegible] of hypertensive patients have increased catechol amines in the urine (von Euler et al, 1954), and none have increased amounts in blood (Raab, 1953) Many patients, also, do not show the exaggerated responses to central vasomotor stimuli, suggesting that they differ in some fundamental manner from those who do.

Perhaps the best way of assessing the relative part that nerves can play in the total vasospastic picture is by cutting them or blocking them. *When surgery or chemical ganglionic blockade is performed on a group of patients, the responses vary from almost none to almost 100 per cent* (Doyle and Smirk, 1955). This variation in response is universal, by all direct or indirect methods used. Therefore, one is forced to the conclusion that there is no universal alteration in sympathetic tone, but that *a variable portion of the vasospasm is sympathetically induced in each patient*, and that the remainder of the vasospasm is the result of other mechanisms.

Nor is this variability apparently dependent upon the sensitivity of arterial muscle, although that is hard to demonstrate. *It is true that* reducing muscular hyperactivity by salt restriction or sodium diuretics enhances the effects of nerve-acting drugs. But only remotely could the two actions, sympathetic hyperactivity and muscular irritability, be connected biochemically.

It is known that certain cations are necessary for nerve transmission Sodium within the nerve, according to one authority (Lorente de Nó, 1949), is necessary for the formation of quaternary ammonium compounds which revert to tertiary nitrogen with the discharge of energy for nerve transmission. The nerve deprived of sodium is hypoactive Nerves without their sheaths (autonomic nerves) are more *susceptible* to sodium deprivation than are myelinated nerves. Therefore, by analogy with in vitro experiments, even a slight depletion of body sodium might reduce sympathetic nerve activity, just as it would reduce smooth muscular reactivity Others believe that potassium is necessary for nerve transmission and that reactivity depends upon the ratio of potassium inside and outside the nerve, just as cardiac muscle is affected by this ratio (Jenerick and Gerard, 1953) Discharge of the nerve, like contraction of muscle, is accompanied by loss of potassium

Whatever the final conclusion, one may conjecture with reasonable accuracy that sodium, potassium, and possibly magnesium may be concerned with nerve transmission, that un-

myelinated nerves are more susceptible to changes in extracellular cations than are myelinated nerves, and that nerve activity may be altered by alterations in ratios of cations outside and inside the nerve fiber If that is so, the adrenal cortical steroids may act as regulators of these cations, both in the whole body and within cells.

There is another method by which sympathetic nerves can become overactive in hypertension, and that is by direct stimulation of the brain For a long time it was believed that hypertension was a "psychosomatic disease," for the personalities of hypertensive patients differed from those of normal persons, and it was convenient to think that the pace of modern living imposed stresses upon persons so constituted as to "bottle up" their psychic complexes and express them through discharges of their sympathetic nerves. Not until the advent of therapy did it slowly become evident that *emotional tension, so prevalent in hypertensive persons, was relieved by any surgical or chemical method which caused sustained normotension.* No study of personality has been made to determine whether or not therapeutic normotension is associated with a change in the subnormal assertiveness and obsessive-compulsive tendencies, said to be part of the "hypertensive personality" (Binger et al., 1945), but the tension and anxiety presumably resulting therefrom are relieved.

If the emotional tension which presumably causes sympathetic discharges is not the result of external stimuli, could it be the result of metabolic changes in the brain? It definitely could, although such changes are inferential and the causative pathways theoretical There are increased amounts of primary amines in hypertensive blood These amines, while having vascular effects, may also have direct stimulatory or depressant activity on local areas of brain The cerebral action of *serotonin*, a primary amine, has been well studied, apparently it is an effector substance for the posterior hypothalamic pathways from cortex *Epinephrine* and *norepinephrine* are also very likely mediators of certain areas of cerebral activity, and both *tyramine* and *isoamyl amine* are cerebroactive. In fact, the brain contains a considerable amount of monamine oxidase, which deaminates these amines Advantage is taken of both amphetamine and iproniazid as cerebral stimulants; both have the property of inhibiting the activity of monamine oxidase, thus preventing destruction of primary amines and allowing them to act. In any organ where deamination is suppressed by diminished oxygen tension but anaerobic decarboxylation can continue, primary amines can be expected to affect cerebral metabolism *This mechanism, which is actually "somatopsychic," may account for the anxiety and nervous tension so prevalent in hypertensive states.*

One other hypothesis states that the inherited characteristics of the individual are such that he has increased emotional tension. Such hereditary tendencies are not explicable in biochemical terms, although it is known that hereditary or congenital absence of a single enzyme system will cause a specific metabolic disease There is no evidence that hypertensive persons have less monamine oxidase than normotensive ones, nor is such a state of affairs likely on a congenital basis. Personality traits may be inherited, however, and so may the ability to react to stress by vasospasm, one fundamental characteristic of most hypertensive individuals (Schroeder, 1957). But nothing is known about the metabolic changes, or more likely, the anatomic ones, which could result in this common characteristic of man

CHEMICAL METHODS AFFECTING THE METABOLIC ALTERATIONS

Because pharmacology is a branch of biochemistry, and because a few chemical tools are now available which will alter the abnormal cellular metabolism in hypertension to cause the appearance of normality, a discussion of logical therapy is in order Understanding of the basic actions of these chemical agents is at best imperfect, but the principal effects have been well described Although no drug acts on one function without affecting others, and no function so affected fails to react on others, the antihypertensive drugs have, in the main, primary actions which either tend to restore normality or to cause further abnormality which superficially appears more normal.

Agents Acting on Autonomic Nerves. Although not a chemical, probably the best tool

for removing the influence of the sympathetic nerves is the surgeon's knife. It is not always the most effective because nerve trunks vary widely in their origins from various ganglia, sensitization to humoral sympathetic effector substances occurs within a few days after the resection unless only preganglionic nerves are severed, and the ability of sympathetic trunks to regenerate is remarkable The more extensive the sympathectomy, the higher is the percentage of favorable results In all types, the innervation of the kidneys is severed. Extent has included anterior root section affecting 4 to 8 dorsal ganglia (Page and Heuer, 1937), supradiaphragmatic sympathectomy affecting 5 to 7 (Peet, 1935), lumbodorsal affecting 8 to 11 (Smithwick, 1940), and subtotal affecting 15 or more (Grimson, 1941) At best, the percentage of "cures" of the disease amounts to about one-third, attesting to the dual pathogenetic pathways present in most cases

Against this background, "reversible chemical sympathectomy at the ganglionic synapse" has been achieved with *ganglionic blocking agents*

These drugs are believed to compete with acetylcholine, preventing synaptic transmission of nerve impulses, and thus may be considered as antimetabolites Most of them are quaternary ammonium compounds (as is acetylcholine), one (mecamylamine and its derivatives) contains tertiary nitrogen Unfortunately, they also block acetylcholine transmission of parasympathetic impulses

The percentage of good control of hypertension (strict normotension) achieved by this form of sympathectomy is about equal to that following extensive surgical measures, again attesting to the duality of pathogenetic influences

No strictly adrenolytic or sympatholytic agent is now available which affects hypertension favorably without intolerable side effects Thus, there is no antimetabolite for norepinephrine useful in hypertension

Stimulation of the carotid sinus and aortic depressor nerves by *veratrum* and its derivatives causes intermittent depression of blood pressure The nature of the chemical reaction involved is not known.

Cerebral sympathetic centers are depressed by *reserpine* and its analogues, chemical cousins to yohimbine

Something is understood of the mode of action of reserpine Tracts from the cerebral cortex to the posterior hypothalamus (the central sympathetic center) are blocked in some manner by which certain primary amines, notably serotonin (5-hydroxytryptamine), epinephrine, and norepinephrine are removed from brain substance (Brodie et al., 1957). Serotonin is also removed from platelets and intestinal wall (Shore et al., 1956). Although the drug does not remain in the tissues, blockade lasts for hours or days. The total effect of tolerable amounts of this form of blockade on the somatic portion of the sympathetic system is relatively minor.

Agents Acting on Adrenal Cortex. Experimental antimetabolites to desoxycorticosterone (DOC) are known An antialdosterone would be a most valuable agent One anti-DOC, which prevents DOC and salt hypertension in rats (Stafford et al., 1953), has been used in a few selected human beings with favorable results on blood pressure, in fact, in one instance following a series of injections, intravenous norepinephrine was required for several days to maintain normal blood pressure in a severely hypertensive woman. The material is irritating to the tissue when injected and has been abandoned Another anti-DOC has recently been used to lower blood pressure in rats with three types of experimental hypertension (Sturtevant, 1957) Further work along this line will be rewarding.

Depletion of body sodium does not depress the adrenal cortex All the evidence is to the contrary, i.e., depletion stimulates the cortex and promotes hypertrophy of the zona glomerulosa (Deane et al., 1948), where aldosterone is believed to be formed

Agents Acting on Sensitivity of Vascular Muscle. There are two types, the first affecting smooth muscular sensitivity indirectly by causing bodily depletion of sodium or other electrolytes, and the second having a more direct action, on muscle itself, on circulating vasoconstrictor substances, or on both

Depletion of body sodium by lowering the intake to very small amounts lessens the reactivity of the blood vessels to epinephrine and norepinephrine even when DOC is given (Raab, 1953) By analogy, this action could be considered to occur even if the amount of

myelinated nerves are more susceptible to changes in extracellular cations than are myelinated nerves, and that nerve activity may be altered by alterations in ratios of cations outside and inside the nerve fiber If that is so, the adrenal cortical steroids may act as regulators of these cations, both in the whole body and within cells.

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bee, 1958). In some manner not understood, this alteration sets in motion the *renal pressor mechanism*, with release of peptide pressor material into the blood stream. The result is further vasoconstriction, now on a humoral pressor mechanism acting directly on vascular smooth muscle. The vasoconstriction, which would be intermittent were it mediated solely through nerves, becomes steady and continuous. If it began through the mediation of renal vascular lesions, it would be expected to be continuous from the onset. In these terms, then, a major vicious circle is initiated by reduction of renal blood flow or renal hypoxia from either nervous or anatomic causes.

Normal vascular smooth muscle becomes sensitized both to nervous impulses and presumably to peptide constrictors by alterations in the gradient of simple bulk cations These alterations are initiated by overproduction of mineralocorticoids Overproduction may be great, as a result of an active adrenal cortical adenoma (primary aldosteronism), or, more commonly, slight, as a result of a physiologic response to renal loss of sodium The loss of sodium is most likely a local metabolic defect resulting from hypoxia and the slight change of renal tissue from aerobic to anaerobic metabolism Thus, a minor "vicious circle" is established, initiated by renal loss of salt and resulting in increased vascular sensitivity.

This change of renal metabolism allows some primary amines to enter the general circulation. There, they probably have some vascular effects, but mainly they *alter the metabolism of brain* The result may be tension, anxiety, and increased cerebral activity leading to greater outflow from the hypothalamus down the sympathetic nerves In this manner, a theoretical minor vicious circle is established by diminution of renal deamination from hypoxia, causing increased nervous activity and its resultant somatic discharges.

The manner by which these vicious circles may be started, eventually causing disease, is unknown. Depending upon one's own viewpoint, one may enter them at several points. Via the brain, hypertension becomes a psychosomatic disease, a result of the *Sturm und Drang* of modern life, or a functional brain disorder. Via the adrenal glands, it becomes a result of an unexplained hypercorticism. Via the kidneys, it is the manifestation of renal vascular disease, developing in the small vessels in some unknown manner, or in the large, from atherosclerosis.

As we have intimated, human cases of hypertension can be found which illustrate all these initiating causes But the majority of cases, lumped together as "essential" hypertension, do not clearly show any of these causes

In strictly biochemical terms, the renal accumulation and storage with age of a *substance which would produce the enzymatic* alterations of hypoxia would initiate these vicious circles quite ideally. Likewise, *progressive deficiency* of a substance, either actual or *conditioned*, which normally acts to *metabolize primary amines and peptide vasoconstrictors would likewise* initiate these vicious circles Certain trace metals have been believed to be directly concerned. Hypertension *can be produced* by several methods and treated successfully by several drugs and procedures While hypertension should be considered *the result* of enzymatic imbalances in one or more specific organs (the kidney being the most likely), its exact biochemical pathogenesis still remains obscure.

aldosterone produced were increased by sodium depletion.

Depletion of body sodium by diuretics should be expected to accomplish the same result. Mercurial diuretics exhibit some such effect (Heider et al., 1958). Chlorothiazide, a new sodium diuretic, which also acts upon potassium, has the same effect as severe restriction of salt (Taggart, 1958). It probably inhibits renal carbonic anhydrase (Beyer, 1958).

Both these methods enhance the activity of agents acting on nerves, suggesting that their primary action is indirect (i.e., on sodium or other cations in smooth muscle). Neither causes reversal of the hypertensive process in more than a small percentage of cases, again suggesting the duality of pathogenic influences.

The second type of agent is characterized by *hydralazine*, a member of a group of antihypertensive chelating agents.

More is known about the biochemical activity of hydralazine than of that of any of the other drugs (Schroeder, 1957). It chelates iron, copper, vanadium, manganese, nickel, silver, mercury, and tin. It forms a complex with some carbonyl groups and with sulfhydryl. It binds certain proteins and polypeptides, including hypertensin. It reacts with certain enzymes in vitro, enhancing the activity of monamine oxidase quite markedly (which would theoretically increase the destruction of primary amines). It is an antienzyme for DOPA decarboxylase and histaminase.

It weakly blocks most simple vasoconstrictor primary amines in the intact animal but strongly inhibits the pressor actions of pherentasin and vasopressin. On the isolated strip of rabbit aorta it weakly inhibits primary amines but strongly abolishes constriction caused by hypertensin and pherentasin. In vascular beds of animals, it dilates constricted vessels, whatever the cause of the constriction, but does not further affect dilated vessels. In hypertensive man, it is the only known drug which dilates the vessels of the kidney.

When hydralazine is given to patients and blood pressure is lowered to normal, pherentasin, previously detected in blood, disappears (Schroeder et al., 1955). Hydralazine alone, however, seldom causes normotension unless an agent acting on nerves is used concomitantly.

Other drugs which destroy the activities of hypertensin and pherentasin in vitro and are antihypertensive in man are thiocyanate, nitroprusside, dimercaptopropanol (British antilewisite), ethylenediaminetetraacetate (EDTA), and azide, all agents capable of chelating or binding trace metals. Because of this common property, not shared by the drugs acting on nerves, it is believed without definitive proof that hypertensin and pherentasin contain a trace metal chelated to the polypeptide, and that trace metals are concerned in hypertension. Actually, hypertensive urine contains many times the normal amount of cadmium.

Because of dual or triple pathogenetic influences acting in most cases of human hypertension, dual or even triple therapeutic tools must be used in order to achieve complete reversal of the process. Clinical results bear this out (Schroeder et al., 1954).

INTERACTION OF THE BIOCHEMICAL ABNORMALITIES

It is not the purpose of this discussion to set up a theoretical although logical system of the pathogenesis of human hypertension. Definition of the pathways by which these local metabolic alterations can interact, however, provides a framework upon which any theory can be based, and further illustrates essential "vicious circles" which appear to operate and which can now be broken by appropriate therapy.

Sympathetic nerves act to constrict arterial smooth muscle through their chemical mediator, *norepinephrine*. Therefore, excessive nervous activity or excessive amounts of norepinephrine (as in certain pheochromocytomas) will constrict the vascular bed generally.

The *kidneys* take part in the general vasoconstriction to a greater extent than do other vascular beds (Smith, 1943), causing reduction in renal plasma flow and, presumably, some degree of hypoxia. *Vascular lesions* (pyelonephritis, glomerulonephritis, atherosclerosis, etc.) can also produce reduction of renal plasma flow and some degree of hypoxia—unless the effective blood pressure rises enough to counteract the lessened flow. Since the kidney has one of the highest oxygen consumption rates of any organ, presumably reduction of blood flow will cause partial conversion from aerobic to anaerobic metabolism (Hucka-

pathologic process in some organ, it follows that the resultant hypertension usually is *secondary* to whatever determines the increased peripheral vascular resistance Instead of dividing hypertension into primary and secondary types, therefore, it might be better to speak of *specific* and *nonspecific* types, the former consisting of those cases in which the etiology is considered to be known This would apply particularly to the hypertension associated with an abnormality of an endocrine organ (a pheochromocytoma of an adrenal gland, for example) or with renal disease, such as glomerulonephritis, bilateral congenital cystic disease, pyelonephritis, hydronephrosis, glomerulosclerosis, lupus, amyloidosis, or periarteritis nodosa. In the case of hypertension accompanied by obvious renal disease, the renal origin of the hypertension has always been accepted, even though the ultimate cause of the elevated blood pressure is still unknown The nonspecific group would consist of those cases in which the cause is still unknown, so-called essential hypertension

PATHOGENESIS

If there is any single fact about the pathogenesis of true hypertension upon which all investigators are agreed, it is that the elevated diastolic blood pressure (the criterion of true hypertension) is due mainly to increased peripheral vascular resistance It is conceded also that such an increase of vascular resistance could occur only on the basis of either widespread obliterative organic disease, or spasm, of the smallest arteries and arterioles That the organic disease of the vessels is ever so severe and so widespread throughout the systemic circulation as to constitute a mechanical reason for increased peripheral vascular resistance is doubtful, so the ultimate cause, *in nearly all cases*, is mainly *functional*, i e, *generalized arteriolar vasospasm secondary either to neurogenic or to endocrinogenic or other humoral stimuli* Since the volume and viscosity of the blood remain constant under most conditions, the only possible variables which can affect the blood pressure are the force and output of the heart and the peripheral vascular resistance, and it is the adjustment between these variables which determines the final blood pressure In those cases in which an endocrine organ is involved, for example, peripheral arteriolar spasm caused by a specific pressor hormone has always been accepted as the main pathogenetic mechanism, although a direct effect upon the heart may also play a part. It is for the group classified as essential hypertension that even the site of the initiating pathologic change is not definitely established, and although vascular disease or some other pathologic process is found in the kidneys of almost 100 per cent of the patients with essential hypertension who come to autopsy, yet the *renal origin* of the hypertension has been strongly contested.

ESSENTIAL HYPERTENSION—THE BENIGN PHASE

By definition, the benign phase of essential hypertension signifies "persistently elevated blood pressure of unknown origin not accompanied by significant renal excretory functional disturbance" Because there is *no obvious* renal disease which can be determined clinically, there has been considerable resistance to the idea that this form of hypertension nevertheless may be of renal origin That other conditions may play a part has never been denied even by those who believe in its renal origin It is true that in a high percentage of the cases of human essential hypertension there is at least a *family history* of the condition. Inherited predisposition to elevated blood pressure is supposed to consist of an abnormal response of the arterioles to constricting stimuli; the cold-pressor test is one of the ways in which this has been determined. Of course, the inherited factor could also be the predisposition to the development of the arteriolar sclerosis, whatever the specific cause of that may be. It is certainly well established that in families in which the blood pressure of the parent is normal, the development of hypertension in the offspring is not nearly so frequent as in those in which both parents have had hypertension.

The indications are that *females are more frequently affected than males*. This is especially true for the malignant phase of hypertension, and may be accounted for by the much more common occurrence of other renal diseases complicating the existing renal vascular sclerosis Most prominent among these complicating renal diseases is *pyelonephritis*, especially in females, both in childhood and in

5

Mechanism of hypertension

HARRY GOLDBLATT

Systemic hypertension is an abnormal condition of great social and economic significance, mainly by reason of pathologic changes in the brain, heart, and kidneys resulting from the vascular disease associated with it. As an indirect cause of disability or death, it ranks first in the list of crippling conditions. True hypertension, which implies persistent elevation of diastolic as well as of systolic blood pressure, is one of the most common clinical signs of disease involving the cardiovascular system, and is perhaps the most frequent functional derangement of the body. In the United States, at least 50 per cent of persons over 50 years of age have hypertension of various origin and, directly or indirectly, elevated blood pressure plays a part in at least 25 per cent of all deaths in that age period. There is some indication that the trend is still upward.

HIGH BLOOD PRESSURE

The upper limits of blood pressure now considered normal are higher than those of 25 years ago. Today, a systolic blood pressure of 140 mm Hg and a diastolic pressure of 90 mm are generally accepted as the upper limits of normal for an adult of either sex, at age 40. Below and above this age, the trends are lower and higher, respectively. The elevation of the diastolic blood pressure is the more indicative of the state of true hypertension, but when there is an elevation of diastolic pressure, there is nearly always a corresponding elevation of the systolic pressure, to such a degree that there is also an increase of pulse pressure. There is such a thing as elevated systolic blood pressure alone, but it depends mainly upon increase of cardiac output and is not the result of increased peripheral vascular resistance. It occurs most commonly in association with endocrine disturbance, such as hyperthyroidism, with abnormal arteriovenous communication, or with arteriosclerosis limited to the aorta and large arteries, in all of which the "runoff" is normal. These are not examples of true hypertension, as defined above. Normally, the diastolic blood pressure is maintained at a certain level, mainly as a result of the intermittent input of blood into the vascular bed, and the resistance to the onflow of blood through the arterioles, i.e., the peripheral vascular resistance. Among the conditions which influence this relationship between the two are nervous stimuli which originate in various sites (carotid and aortic sinuses) and which influence the cardiac and vasomotor centers, endocrine secretions, and the natural tone of the peripheral arterioles.

CLASSIFICATION

Hypertension has been classified as primary and secondary, but, strictly speaking, the only circumstance in which the elevated blood pressure might well be considered *primary* would be if the increased peripheral vascular resistance were due only to an increase of the inherent tone of the arterioles. There is no other good reason for using the word "primary," unless it be in the sense of unknown origin, and for this the term "essential" has already been appropriated. Since peripheral vasospasm and the increased peripheral vascular resistance are nearly always caused by a

dog in 2 or 3 days, when hypertension and renal insufficiency are produced by excessive constriction of both main renal arteries In man, the malignant phase may occur as a result of pronounced obliterative arterial and arteriolar sclerosis, but more commonly it develops when excretory failure occurs as a result of the development of some complicating pathologic condition in a kidney which was previously the seat of arteriolar disease

The most common of these renal complications, the importance of which has not been stressed adequately because it is an insidious disease which is frequently overlooked clinically, is chronic interstitial nephritis (*pyelonephritis*) which, when sufficiently severe, brings about the excretory failure of kidneys, previously the seat of only arterial and arteriolar sclerosis. Other complicating renal diseases which may have the same effect as pyelonephritis are *glomerulonephritis*, *glomerulosclerosis*, the glomerular lesions of *lupus*, *periarteritis nodosa*, and *amyloidosis*, which when superimposed upon renal arterial and arteriolar sclerosis of even moderate degree, bring about the malignant phase Less commonly, the malignant phase occurs as a result of the development of arteriolosclerosis in an individual with a previously existent chronic bilateral pyelonephritis The importance of the part played by *interstitial nephritis* as one of the possible causes of malignant hypertension cannot be stressed too greatly, because it promises possible treatment, and even prevention, of the most common pathologic condition responsible for bringing about the change from the benign to the malignant phase of essential hypertension

EXPERIMENTAL RENAL HYPERTENSION

On the basis that the development of obliterative vascular disease precedes the occurrence of essential hypertension in man, and that the elevation of the blood pressure does not occur until, and unless, the kidneys are involved, experiments were devised by the author to test whether or not the vascular disease alone could be the primary factor in the elevation of the blood pressure Because it was not possible to reproduce the arterial and arteriolar sclerosis, it was decided to constrict the main renal arteries, in the hope that this procedure might reproduce the disturbance of intrarenal hemodynamics which undoubtedly results from the intrarenal vascular disease.

In the dog, moderate constriction of only one main renal artery by means of a silver clamp devised for the purpose resulted in an elevation of blood pressure which began within 24 hr, increased for a week or longer, remained elevated at the maximum level for about 2 or 3 weeks, and then usually returned to normal in about 4 to 6 weeks. Only rarely did it remain elevated much longer. In the rat, the rabbit, the sheep, and the goat, however, it remained elevated for many months. The removal of the ischemic kidney at the height of the hypertension resulted in a prompt fall of the blood pressure to normal The development of elevated blood pressure as a result of constriction of only *one* main renal artery, and the prompt return of the blood pressure to normal when the ischemic kidney was removed, led to the recognition of the existence of cases of human hypertension associated with *unilateral renal disease* and the return of the blood pressure to normal as a result of the removal of the diseased kidney in those cases in which the contralateral kidney proved to be normal Homer Smith (1956), in a review of the literature up to the end of 1956, reported a cure of the hypertension in 149 out of 575 cases (26 per cent) of essential hypertension in which the existence of unilateral renal disease was recognized and the diseased kidney was removed Thompson, in a report of similar cases operated upon at the Mayo Clinic, reported a cure of the hypertension in 50 per cent of the patients with unilateral renal disease, when the renal disease proved to be an atrophic kidney, probably the seat of vascular disease and pyelonephritis It does not seem [illegible]

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Moderate constriction of *both* main renal arteries, or moderate constriction of one main renal artery and contralateral nephrectomy, resulted in the development of persistent hypertension in animals. The successful production of persistent hypertension, first in the dog, and later in a variety of animals, by a

adult life, most frequently in association with pregnancy.

In so far as age is concerned, there are data which show definitely that the trend after the age of 40 years is upward and that the incidence of essential hypertension is relatively low before 40.

Although hypertension usually is considered to be of infrequent occurrence in Orientals and in African Negroes, yet the incidence of hypertension in the pure Negro of the Virgin Islands, for example, is unusually high. It may be of special interest that in the kidneys of two patients from these islands with so-called essential hypertension, which the author had an opportunity to examine, there was severe diffuse intrarenal, especially preglomerular, arteriolar sclerosis. The effect of *environment* is intangible, and although much has been written about psychoneurogenic effects of the *stress* of modern living conditions, yet it is almost impossible to establish with certainty any direct relationship between these and the peripheral vascular disease or the persistent hypertension. At autopsy, in cases of human, benign, essential hypertension, arterial and arteriolar sclerosis is present in many organs and in variable amount, but it has been shown that it is most pronounced and most frequent *in the kidneys* of such individuals, although it has been demonstrated clearly also that the kidney is the organ least vulnerable to vascular sclerosis. Most investigators, at least prior to 1930, have interpreted this to mean that the elevated blood pressure comes first and that the vascular disease in all tissues, including the kidneys, is a consequence of the persistent stretching of the wall of the blood vessels by the elevated intravascular pressure, or the result of persistent vasospasm On the contrary, the author's interpretation is that the hypertension does not develop until the kidneys are involved, whatever the cause of the vascular disease may be.

ESSENTIAL HYPERTENSION—MALIGNANT PHASE

The most recent acceptable definition of malignant hypertension (Medical Advisory Board of the Council for High Blood Pressure of the American Heart Association) reads as follows.

A clinical phase, rarely occurring *de novo*, more often appearing after a primary or secondary hypertension, characterized by diastolic hypertension and by accelerated and progressive renal damage, usually (but not necessarily) accompanied by papilledema, often by retinal hemorrhages and "exudate" and giving rise to death from uremia, unless the course is terminated along the way by complicating brain or heart damage.

There have been great differences of opinion about the pathogenesis of this phase of hypertension. Some consider it to be a form of essential hypertension, not primarily of renal origin but marked by impairment of renal excretory function which occurs as a late or terminal manifestation; others (including the author) believe that the malignant phase, like the benign, is primarily, and even more obviously, of renal origin. There are good reasons, experimental, pathologic, and clinical, for this wide difference of view. A chief reason has been the failure of many investigators to recognize that the pathologic changes in the kidneys in the malignant phase are neither uniform nor unique. Another reason has been the difference of opinion about the nature and the pathogenesis of the necrotizing arteriolar lesion which has been regarded as pathognomonic of this condition.

A common error has been the belief that the *arteriolar fibrinoid degeneration and necrosis*, with or without perivascular inflammation, usually considered pathognomonic of malignant hypertension, represent an accelerated form of arteriolosclerosis There are no morphologic or pathogenetic reasons for the confusion of this lesion with arteriolosclerosis Another belief has been that arteriolar necrosis is so diffuse and so severe in the kidneys that it is actually the cause of the renal failure, when it develops in a person with previously benign hypertension This belief is not based upon substantial evidence As a matter of fact the arteriolar necrosis involving the kidneys is a sporadic, variable, secondary, and usually terminal manifestation of the malignant phase of essential hypertension It is sometimes difficult to find any of these lesions, although occasionally they may be abundant. Exactly what it is that brings about the fibrinoid necrosis of previously normal or sclerotic arterioles is not known It can develop in the arterioles of the

dog in 2 or 3 days, when hypertension and renal insufficiency are produced by excessive constriction of both main renal arteries. In man, the malignant phase may occur as a result of pronounced obliterative arterial and arteriolar sclerosis, but more commonly it develops when excretory failure occurs as a result of the development of some complicating pathologic condition in a kidney which was previously the seat of arteriolar disease

The most common of these renal complications, the importance of which has not been stressed adequately because it is an insidious disease which is frequently overlooked clinically, is chronic interstitial nephritis (*pyelonephritis*) which, when sufficiently severe, brings about the excretory failure of kidneys, previously the seat of only arterial and arteriolar sclerosis Other complicating renal diseases which may have the same effect as pyelonephritis are *glomerulonephritis*, *glomerulosclerosis*, the glomerular lesions of *lupus*, *periarteritis nodosa*, and *amyloidosis*, which when superimposed upon renal arterial and arteriolar sclerosis of even moderate degree, bring about the malignant phase Less commonly, the malignant phase occurs as a result of the development of arteriolosclerosis in an individual with a previously existent chronic bilateral pyelonephritis The importance of the part played by *interstitial nephritis* as one of the possible causes of malignant hypertension cannot be stressed too greatly, because it promises possible treatment, and even prevention, of the most common pathologic condition responsible for bringing about the change from the benign to the malignant phase of essential hypertension.

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Moderate constriction of both main renal arteries, or moderate constriction of one main renal artery and contralateral nephrectomy, resulted in the development of persistent hypertension in animals. The successful production of persistent hypertension, first in the dog, and later in a variety of animals, by a

method which most closely simulates the probable hemodynamic state of the kidney of essential hypertension, confirmed the assumption that it is the intrarenal vascular disease which causes human essential hypertension. The fact that, as in human essential hypertension, a disturbance of renal excretory function was not a necessary accompaniment of this type of experimental hypertension is considered additional important, indeed essential, evidence for the possible identity of these hypertensive states in man and the experimental animal The nature of the hemodynamic disturbance produced in a kidney by moderate constriction of a main renal artery has not been determined with certainty in all stages of the hypertension which results from this procedure, but it is probably similar to that of the nephrosclerotic kidney so frequently found at autopsy in cases of human essential hypertension By direct means, immediately after constriction of the main renal artery in the dog, it was shown that there was definite reduction in the blood flow through the kidney, and, by indirect means (inulin clearance), it has been shown that the reduction of renal blood flow, without reduction, or even with an actual increase, of intraglomerular pressure, and with maintenance of normal excretory function, can be found in most individuals with early benign human essential hypertension The results of the large number of investigations carried out after the successful production of experimental renal hypertension in animals indicate that human essential hypertension also may be of renal origin The main reasons in favor of this view may be summarized briefly as follows

SUMMARY OF THE EVIDENCE IN FAVOR OF THE RENAL ORIGIN OF HUMAN ESSENTIAL HYPERTENSION

In most cases of human essential hypertension, there is found at autopsy either renal arterial and arteriolar sclerosis only (the unscarred kidney), or true nephrosclerosis (the scarred kidney), or some other obvious extrarenal or intrarenal lesion which probably produces the same hemodynamic disturbance in the kidney as is produced by intrarenal obliterative vascular sclerosis This is true despite the fact that, of all organs in the body, the vascular bed of the kidney is the least vulnerable to the development of arteriolosclerosis

In animals, it is possible to constrict both main renal arteries just enough to bring about the development of hypertension without significant impairment of renal excretory function. Even moderate constriction of one main renal artery and contralateral nephrectomy may be followed by the development of persistent hypertension without significant impairment of renal excretory function.

In most patients with benign essential hypertension, there is some reduction of the flow of blood through the glomeruli, similar to that produced by moderate constriction of the main renal artery in hypertensive animals.

Great constriction, without occlusion, of both main renal arteries, or great constriction of one main renal artery and contralateral nephrectomy or contralateral occlusion of the ureter, results in elevation of blood pressure, definite impairment of renal excretory function, and the development of the necrotizing arteriolar lesions characteristic of the malignant phase of essential hypertension.

Hemodynamically, the state of an animal with experimental renal hypertension, in both the benign and malignant phases, is in all respects like that of the corresponding phases of human essential hypertension In animals, moderate constriction of the main artery of one kidney results in a rise of blood pressure which, in the dog, usually persists for from 4 to 6 weeks, but which in the rat, rabbit, sheep, and goat may persist for many months In man, also, partial obstruction of the main artery of only one kidney by an embolus or thrombus, or by pressure upon, or kinking of, the main renal artery, has been followed by the development of persistently elevated blood pressure

In animals with benign hypertension for as long as 8 years, the only significant anatomic alterations found at autopsy have been moderate cardiac hypertrophy and medial thickening of the arteries and arterioles due to hypertrophy and hyperplasia of the smooth muscle cells Simple intimal arteriosclerosis or hyalinizing arteriolar sclerosis did not develop in animals as a result of pronounced hypertension for many years Cardiac failure, coronary thrombosis, and cerebral hemorrhage did not occur in animals, for they did not develop coronary or cerebral arteriosclerosis. This is an indication that in man the vascular disease

probably precedes the development of the persistent hypertension, which happens only when the kidneys also become the seat of arterial and arteriolar sclerosis. This does not ignore or exclude the fact that, at least in some human beings, the labile type of neurogenic or endocrinogenic elevation of blood pressure may *occur* before the fixed and persistent hypertension develops as a result of the vascular disease of the kidneys. This is not to say that the vascular disease is a direct consequence of the previously elevated blood pressure. The contention of Byrom and Dodson that hypertension alone can produce even the necrotizing arteriolar lesion of the malignant phase of hypertension has not been confirmed. There is *no proof that* psychoneurogenic hypertension actually plays a part in the pathogenesis of the vascular disease in man, or that it is a necessary precedent of essential hypertension.

In many cases in which a diagnosis of essential hypertension had been entertained at first, the occasional existence of unilateral renal disease has now been recognized. The fall of the blood pressure which has resulted from the removal of the diseased kidney or restoration of the normal circulation to the kidney can be explained only on the basis that the kidney—the victim of either vascular sclerosis or some other abnormal condition which produces the same intrarenal hemodynamic disturbance—is the source of a substance which, in some way, induces the development of the hypertension.

Aortograms in the living patient, and careful investigation of the renal arteries and aorta at the site of origin of the renal arteries, at autopsy, have revealed stenosis in various portions of one of the main renal arteries, or in both of them, including their site of origin from the aorta, as a result of atherosclerosis, *simple* intimal fibrosis, or fibroelastosis, in cases otherwise regarded clinically as typical examples of human essential hypertension. These lesions have the effect of a clamp on the renal artery, in so far as the kidney is concerned. In some cases of this kind in which the vascular abnormality has been recognized in life, excision of the involved portion of the blood vessels and transplantation of the arteries, or the insertion of an arterial graft have been used to restore the circulation to such a kidney or kidneys, and the elevated blood pressure has returned to normal when there was no significant intrarenal arterial or arteriolar disease, or any other pronounced pathologic process within the kidney.

In experimental renal hypertension, all evidence is in favor of a humoral mechanism of renal origin as the cause of the elevated blood pressure.

Renin, an enzyme from the kidney, acts upon *angiotensinogen*, the substrate in the plasma, to produce *angiotensin*, a polypeptide, which is the effective vasoconstrictor substance that induces the vasospasm and an increase in peripheral vascular resistance. An increased amount of this substance has been *demonstrated* in the blood of hypertensive man and animals. But in animals with experimental renal hypertension for years, and in human beings in the chronic benign phase, there is only a slightly elevated angiotensin content in the blood, although, even at this late stage, the blood pressure of hypertensive animals can be brought down to normal by the parenteral injection of *renin* and the production of an adequate quantity of *antirenin* in the blood. This has not been possible in man because, with the exception of the *renin* of monkeys and anthropoid apes, no heterologous antirenin will inactivate human renin.

In *hypertensive* dogs, the development of accessory circulation to the kidneys by their transplantation into the spleen, or by wrapping them in omentum or muscle, results in a fall of blood pressure to normal. In human hypertension, however, this procedure probably would not be effective because the obliterative vascular disease is almost always intrarenal, therefore the production of accessory circulation through the cortex in hypertensive human beings would probably not improve the circulation of the functioning components of the kidney.

There is no convincing evidence that hypertension, *per se*, is the cause of arterial or arteriolar sclerosis in the brain, heart, and kidney, but it is recognized that the existence of hypertension in an individual with vascular disease greatly jeopardizes life. Cardiac failure and rupture of a myocardial infarct are more likely to occur in a hypertensive individual who develops occlusive coronary disease. Similarly, cerebral hemorrhage is more likely to occur in a hypertensive person with cerebral vascular sclerosis. Aneurysms of an arteriosclerotic aorta and of large vessels are also more

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In animals with benign hypertension for as long as 8 years, the only significant anatomic alterations found at autopsy have been moderate cardiac hypertrophy and medial thickening of the arteries and arterioles due to hypertrophy and hyperplasia of the smooth muscle cells Simple intimal arteriosclerosis or hyalinizing arteriolar sclerosis did not develop in animals as a result of pronounced hypertension for many years Cardiac failure, coronary thrombosis, and cerebral hemorrhage did not occur in animals, for they did not develop coronary or cerebral arteriosclerosis. This is an indication that in man the vascular disease

probably precedes the development of the persistent hypertension, which happens only when the kidneys also become the seat of arterial and arteriolar sclerosis. This does not ignore or exclude the fact that, at least in some human beings, the labile type of neurogenic or endocrinogenic elevation of blood pressure may occur before the fixed and persistent hypertension develops as a result of the vascular disease of the kidneys. This is not to say that the vascular disease is a direct consequence of the previously elevated blood pressure. The contention of Byrom and Dodson that hypertension alone can produce even the necrotizing arteriolar lesion of the malignant phase of hypertension has not been confirmed. There is no proof that psychoneurogenic hypertension actually plays a part in the pathogenesis of the vascular disease in man, or that it is a necessary precedent of essential hypertension

In many cases in which a diagnosis of essential hypertension had been entertained at first, the occasional existence of unilateral renal disease has now been recognized The fall of the blood pressure which has resulted from the removal of the diseased kidney or restoration of the normal circulation to the kidney can be explained only on the basis that the kidney—the victim of either vascular sclerosis or some other abnormal condition which produces the same intrarenal hemodynamic disturbance—is the source of a substance which, in some way, induces the development of the hypertension

Aortograms in the living patient, and careful investigation of the renal arteries and aorta at the site of origin of the renal arteries, at autopsy, have revealed stenosis in various portions of one of the main renal arteries, or in both of them, including their site of origin from the aorta, as a result of atherosclerosis, simple intimal fibrosis, or fibroelastosis, in cases otherwise regarded clinically as typical examples of human essential hypertension These lesions have the effect of a clamp on the renal artery, in so far as the kidney is concerned In some cases of this kind in which the vascular abnormality has been recognized in life, excision of the involved portion of the blood vessels and transplantation of the arteries, or the insertion of an arterial graft, have been used to restore the circulation to such a kidney or kidneys, and the elevated blood pressure has returned to normal when there was no significant intrarenal arterial or arteriolar disease, or any other pronounced pathologic process within the kidney.

In experimental renal hypertension, all evidence is in favor of a humoral mechanism of renal origin as the cause of the elevated blood pressure.

Renin, an enzyme from the kidney, acts upon *angiotensinogen*, the substrate in the plasma, to produce *angiotensin*, a polypeptide, which is the effective vasoconstrictor substance that induces the vasospasm and an increase in peripheral vascular resistance. An increased amount of this substance has been demonstrated in the blood of hypertensive man and animals. But in animals with experimental renal hypertension for years, and in human beings in the chronic benign phase, there is only a slightly elevated angiotensin content in the blood, although, even at this late stage, the blood pressure of hypertensive animals can be brought down to normal by the parenteral injection of renin and the production of an adequate quantity of *antirenin* in the blood. This has not been possible in man because, with the exception of the renin of monkeys and anthropoid apes, no heterologous antirenin will inactivate human renin.

In hypertensive dogs, the development of accessory circulation to the kidneys by their transplantation into the spleen, or by wrapping them in omentum or muscle, results in a fall of blood pressure to normal In human hypertension, however, this procedure probably would not be effective because the obliterative vascular disease is almost always intrarenal, therefore the production of accessory circulation through the cortex in hypertensive human beings would probably not improve the circulation of the functioning components of the kidney.

There is no convincing evidence that hypertension, per se, is the cause of arterial or arteriolar sclerosis in the brain, heart, and kidney, but it is recognized that the existence of hypertension in an individual with vascular disease greatly jeopardizes life. Cardiac failure and rupture of a myocardial infarct are more likely to occur in a hypertensive individual who develops occlusive coronary disease Similarly, cerebral hemorrhage is more likely to occur in a hypertensive person with cerebral vascular sclerosis Aneurysms of an arteriosclerotic aorta and of large vessels are also more

method which most closely simulates the probable hemodynamic state of the kidney of essential hypertension, confirmed the assumption that it is the intrarenal vascular disease which causes human essential hypertension. The fact that, as in human essential hypertension, a disturbance of renal excretory function was not a necessary accompaniment of this type of experimental hypertension is considered additional important, indeed essential, evidence for the possible identity of these hypertensive states in man and the experimental animal. The nature of the hemodynamic disturbance produced in a kidney by moderate constriction of a main renal artery has not been determined with certainty in all stages of the hypertension which results from this procedure, but it is probably similar to that of the nephrosclerotic kidney so frequently found at autopsy in cases of human essential hypertension. By direct means, immediately after constriction of the main renal artery in the dog, it was shown that there was definite reduction in the blood flow through the kidney, and, by indirect means (inulin clearance), it has been shown that the reduction of renal blood flow, without reduction, or even with an actual *increase*, of intraglomerular pressure, and *with maintenance* of normal excretory function, can be found in most individuals with early *benign* human essential hypertension The results of the large number of investigations carried out after the successful production of experimental renal hypertension in animals indicate that human essential hypertension also may be of renal origin The main reasons in favor of this view may be summarized briefly as follows

SUMMARY OF THE EVIDENCE IN FAVOR OF THE RENAL ORIGIN OF HUMAN ESSENTIAL HYPERTENSION

In most cases of human essential hypertension, there is found at autopsy either renal arterial and arteriolar sclerosis only (the unscarred kidney), or true nephrosclerosis (the scarred kidney), or some other obvious extrarenal or intrarenal lesion which probably produces the same hemodynamic disturbance in the kidney as is produced by intrarenal obliterative vascular sclerosis. This is true despite the fact that, of all organs in the body, the vascular bed of the kidney is the least vulnerable to the development of arteriolosclerosis.

In animals, it is possible to constrict both main renal arteries just enough to bring about the development of hypertension without significant impairment of renal excretory function. Even moderate constriction of one main renal artery and contralateral nephrectomy may be followed by the development of persistent hypertension without significant impairment of renal excretory function.

In most patients with benign essential hypertension, there is some reduction of the flow of blood through the glomeruli, similar to that produced by moderate constriction of the main renal artery in hypertensive animals.

Great constriction, without occlusion, of both main renal arteries, or great constriction of one main renal artery and contralateral nephrectomy or contralateral occlusion of the ureter, results in elevation of blood pressure, definite impairment of renal excretory function, and the development of the necrotizing arteriolar lesions characteristic of the malignant phase of essential hypertension.

Hemodynamically, the state of an animal with experimental renal hypertension, in both the benign and malignant phases, is in all respects like that of the corresponding phases of human essential hypertension. In animals, moderate constriction of the main artery of one kidney results in a rise of blood pressure which, in the dog, usually persists for from 4 to 6 weeks, but which in the rat, rabbit, sheep, and goat may persist for many months. In man, also, partial obstruction of the main artery of only one kidney by an embolus or thrombus, or by pressure upon, or kinking of, the main renal artery, has been followed by the development of persistently elevated blood pressure

In animals with benign hypertension for as long as 8 years, the only significant anatomic alterations found at autopsy have been moderate cardiac hypertrophy and medial thickening of the arteries and arterioles due to hypertrophy and hyperplasia of the smooth muscle cells Simple intimal arteriosclerosis or hyalinizing arteriolar sclerosis did not develop in animals as a result of pronounced hypertension for many years Cardiac failure, coronary thrombosis, and cerebral hemorrhage did not occur in animals, for they did not develop coronary or cerebral arteriosclerosis. This is an indication that in man the vascular disease

6

Clinical aspects of hypertension

RUSTOM JAL VAKIL

Prevalence. The high incidence and importance of high blood pressure, or hypertension, in the causation of death and disease remain unquestioned. Next to arteriosclerosis, it is the disease with the greatest fatality rate, accounting directly or indirectly for over one-fifth of all deaths and for 25 to 35 per cent of deaths over the age of 50. In the United States alone, it is responsible for over 320,000 deaths per year.

There is no unanimity of opinion, however, about the exact *incidence of hypertension.* Even in the United States, the total number of hypertensive persons has been computed by different observers as 20 million, 15 million, and 6 million, respectively (Robinson and Brucer, 1939). This discrepancy between different estimates is due not to error but to the different criteria adopted in the selection of cases. The borderline between normotensive and hypertensive zones has not as yet been clearly defined.[1]

Hypertension, either primary or secondary, occurs in from 5 to 20 per cent of the entire population, and in over 50 per cent of individuals over the age of 50. Its true incidence is probably higher than that reported in clinical studies, since many cases are completely asymptomatic and blood pressure is not routinely measured. Moreover, many practitioners withhold true figures of blood pressure levels from patients and relatives for fear of causing a "hypertension neurosis."

In most civilized countries, hypertension is one of the most common causes of heart disease, as well as of heart failure, accounting roughly for about 30 per cent of all cardiac patients. In Eastern countries, the incidence of hypertension is probably as high as in Western countries, although severe and malignant forms of the disease are much less common (Vakil, 1950).

Definition. The term *hypertension* or *high blood pressure* connotes a *systemic arterial* pressure consistently above the accepted *normal.* In the past, it was customary to regard all blood pressure readings over 150 systolic and over 90 diastolic as indicative of hypertension (Hines, 1940, Herndon, 1946). In view of the *great influence* of age and sex factors on blood pressure, as demonstrated conclusively by recent observers (Bussek et al., 1946; Gover, 1948, Master et al., 1952), such fixed and unvarying *criteria* for normal blood pressure levels are no longer acceptable.

A blood pressure reading higher than the statistically established average or mean level *need not* be abnormal; it may still be within the normal or physiologic range for the age and sex of the patient. The term *hypertension* must therefore be restricted to levels consistently *higher than the normal maximum level* (NML) rather than the *average or mean level* for a given age and sex. The difference between the recorded high blood pressure level and the maximum *normal level* gives a rough measure of the degree of hypertension and has been termed "pressure load" or "plus pressure" (Vakil, 1954b).

Arterial hypertension is merely a physical finding or sign, like fever or tachycardia, that may result from a variety of disorders. As such, it means no more than an abnormally high

[1] See also Part 3, Chap. 5. *Editor.*

likely to occur in the hypertensive individual. These lesions do not occur in the hypertensive animals because they do not develop the arteriosclerosis.

The only proved secondary changes which occur in any organ directly as a result of elevated blood pressure, in the hypertensive animals, and even in man, are *hypertrophy of the heart* and *thickening of the media* of the arteries. Although there is no proof that the elevated blood pressure per se can initiate and produce arterial sclerosis and arteriolar sclerosis, and indeed there is proof to the contrary, yet there is no unequivocal evidence that when the other condition, or conditions, responsible for the sclerosis is present, the elevated blood pressure may not aggravate or accelerate the sclerosis.

Hypertension accompanied by impairment of renal excretory function (the malignant phase) can occur as a direct result of pronounced obliterative arterial and arteriolar sclerosis, but it occurs more commonly as a result of some other complicating disease of the kidney, notably chronic pyelonephritis, which develops in a kidney already the seat of arterial and arteriolar sclerosis. In animals, this phase can be reproduced by great constriction of the main renal arteries.

It is difficult to avoid the conclusion that the so-called essential hypertension, in both the benign and malignant phases, is of renal origin

disease and ventricular hypertrophy was proved more conclusively by Traube (1856) with the aid of pulse palpation.

Among the complications of hypertension, apoplexy or, cerebral hemorrhage, was first described by Wepfer (1658) in a gouty monk "inclined to anger"; coronary thrombosis, by Bonetus (1700) and by Krehl (1740). The signs of left ventricular hypertrophy in hypertension were described by Laennec (1819), and the high-tension pulse and loud aortic 2d sound of hypertension, by Traube.

The first sphygmomanometer for measuring blood pressure was designed by Herisson in 1830, to be later refined and modified by a host of workers, including von Basch (1893), Potain, and Riva-Rocci (1896), thus inaugurating a new era in the understanding of circulatory hemodynamics

After the pioneer work of Richard Bright, it was customary to regard hypertension as a consequence of either kidney disease or arteriosclerosis, that is, until Mahomed described it as a *precursor* of Bright's disease and von Basch referred to it as *latent arteriosclerosis* The present concept of essential hypertension as an independent entity, not necessarily followed by renal or arterial disease, was developed by Allbutt and Huchard

Another milestone in our growth of knowledge of hypertension was the chemicopathologic study and the classification of nephrosclerosis into benign and malignant forms (Volhard and Fahr, 1914).

Since the introduction of an ancient Indian plant (*Rauwolfia serpentina*) into the Western world (by the author, 1949), immense strides have been made and considerable headway has been gained in the treatment of high blood pressure. Hypertension was once given up as hopelessly irremediable, now innumerable patients with hypertension have been benefited, and at times given a new lease on life, by the introduction of many new antihypertensive remedies, particularly the ganglion-blocking agents and the chlorothiazide derivatives

Pathogenesis HEMODYNAMIC MECHANISMS. Several mechanisms are concerned in the maintenance of normal blood pressure and circulatory homeostasis Functional changes of one or more of these dynamic factors can bring about a transitory or persistent rise of systemic blood pressure: (1) increased cardiac output or minute volume, (2) increased viscosity of the blood, (3) decreased elas-ticity of the ... the blo...

After ... finally established that in the great majority of cases of essential hypertension, the mechan... concerned ... by vaso... ganic n... once postulated by Gull and Sutton in the genesis of hypertension, has been convincingly ruled out.

CAUSE OF VASOCONSTRICTION. The exact nature of the stimulus or factor that brings about the angiospasm remains obscure. It has not as yet been convincingly established whether it is due to excess of a circulating pressor substance (humoral theory), lack of depressor substance (humoral theory), neurogenic reflex mechanism, or increased reactivity of the arterioles (possibly secondary to organic changes), which have become hypersensitive to normal amounts of pressor substance. It is possible that the *initiating mechanism* may not be the same as the *perpetuating mechanism*. It is not even certain whether essential hypertension is a single clinical entity or a collection of entities grouped under one heading

PRESSOR MECHANISMS Since the time of Bright, medical opinion regarding the etiology of hypertension has been constantly vacillating between the theories of renal and extrarenal *origin*. *First* regarded as renal in origin, on the basis of Bright's work, hypertension was then considered to be primary and nonrenal after the studies of Allbutt and Huchard. Goldblatt's experiments with clamping of the renal *arteries of dogs* seemed to substantiate the "renal" theory. More recent studies, however, have again cast doubts on the role of the kidney. Of the many pressor mechanisms implicated in the genesis of essential *hypertension, the following* are of particular interest, according to Fishberg (1954)

THEORIES OF ORIGIN

1. Renal
   - *a*. Renin-angiotensin pressor mechanism (Goldblatt, 1937; Braun-Menéndez, 1939, Page, 1939)
   - *b* Disturbed balance of vasoexciter and vasodepressor mechanisms (Shorr)
   - *c* Juxtaglomerular apparatus (Polkissen) mechanism (Goormaghtigh)
   - *d*. Intrarenal pelvis mechanism (Ravich)
   - *e* Deficiency of antipressor renal principle
2. Peripheral (humoral)
   - *a*. Pressor substance in blood, e g, pherentasin (Schroeder)
   - *b*. Sensitization of arterioles to normal pressor substance
   - *c* Intrinsic alteration of arteriolar wall
3. Endocrine (or glandular)
   - *a* Hypernorepinephrinemia (medullary oversecretion)
   - *b* Overaction of adrenal cortex (hyperadrenocorticism)
   - *c* Pituitary overaction
   - *d*. Gonadal dysfunction
   - *e* Thyroid dysfunction
   - *f* Pancreatic disorder

level of pressure or the exaggeration of a normal biologic phenomenon. When associated, however, with clinical or pathologic manifestations of disease, it should be referred to as *hypertensive disease* or *hypertensive heart disease* (cardiopathy), renal disease (nephropathy), or cerebral disease (encephalopathy), depending on the site of maximum involvement.

True hypertension (arterial or systemic hypertension) implies an elevation of both the systolic and the diastolic blood pressure. When the rise of either pressure happens to be disproportionate, the condition is referred to as either *systolic* or *diastolic* hypertension.

Systolic Hypertension. An isolated elevation of systolic pressure, the diastolic remaining normal or low, is referred to as systolic hypertension. Hemodynamically distinct from true hypertension, it may be of cardiac or aortic origin.

CAUSES

- I. Cardiac (increased left ventricular stroke volume)
  - *A.* Aortic regurgitation
  - *B.* Patent ductus arteriosus
  - *C.* Arteriovenous fistula or aneurysm
  - *D.* Complete heart block
  - *E.* Thyrotoxicosis
  - *F.* Severe anemia
  - *G.* Beriberi
  - *H.* Paget's disease
- II. Aortic (decreased elasticity or distensibility of aorta)
  - *A.* Senile changes of aortic wall
  - *B.* Atherosclerosis or aorta
  - *C.* Coarctation of aorta

The differentiation of systolic from true or diastolic hypertension is of great importance for diagnosis, prognosis, and treatment. A transitory rise of blood pressure, usually systolic, during or after intense emotion (e.g., excitement) or exercise is commonly referred to as *physiologic hypertension*.

Types of Hypertension. Persistent elevation of diastolic and systolic blood pressure levels, in the absence of any demonstrable cause, is referred to as *essential or primary hypertension*. When secondary to an obvious cause or lesion, it is referred to as *secondary or symptomatic hypertension*. Unfortunately, 80 to 90 per cent of cases are of the essential type, the causes remaining obscure in spite of all investigations.

ETIOLOGIC CLASSIFICATION OF HYPERTENSION

- I. *Essential (or primary)*
  - *A.* Benign (about 90 per cent)
  - *B.* Malignant (about 10 per cent)
- II. Secondary (or symptomatic)
  - *A.* Renal (or nephrogenic)
  - *B.* Endocrine
  - *C.* Neurogenic (or cerebral)
  - *D.* Psychogenic
  - *E.* Cardiovascular
  - *F.* Miscellaneous

ESSENTIAL HYPERTENSION

Nomenclature. One of the most frequent causes of death, essential hypertension has been discussed in the medical literature under a variety of designations (Fishberg, 1954), including primary hypertension, benign or malignant sclerosis (Volhard and Fahr), hyperpiesia (Allbutt), presclerosis (Huchard), latent arteriosclerosis (von Basch), essential hypertonia (Frank), and "prealbuminuric stage" of chronic Bright's disease (Mahomed).

Apart from long use and wide acceptance, the term "essential hypertension" has little to recommend it. it is unscientific and far from ideal. The term "primary hypertension" is more informative, in that it indicates the absence of *demonstrable causes*.

Historical Landmarks. The oldest reference to hypertension is accredited by Volhard to the ancient Chinese physician Choun-You (200 B.C.), according to whom a pulse that feels "very firm" on depressing and "very tight" on superficial feeling should suggest kidney disease, an observation that cannot be bettered today after centuries of scientific progress.

The first measurement of arterial blood pressure by the direct method was made by Stephen Hales (1733), who, out of curiosity, introduced a long tube into the femoral artery of a mare and observed pulsations of the ascending column of blood within the tube.

Richard Bright of London commented on the increased resistance to injection offered by arterial vessels in renal diseases (1827). After an exhaustive study of renal disease, he could find no possible cause for the cardiac hypertrophy which he noted in 22 out of 52 cases. One of the two explanations suggested by Bright for the hypertrophy was a change in "the minute and capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system"; in other words, increased peripheral resistance and hypertension. The role of hypertension as the connecting link between Bright's

become normal after medical treatment of hypertension.

The general correlation between high blood pressure and the 24-hr output of urinary sodium tends to persist even after lowering of the arterial pressure by medical or surgical means (Green and Ellis, 1954). Whether the natriuresis of hypertension is primary and conducive to the development of hypertension or is secondary to the renal involvement of hypertensive disease remains conjectural (Cottier et al, 1958).

The distribution of sodium in the body is perhaps of greater etiologic significance in hypertension than the total amount of sodium in the body. Abnormally high amounts of sodium have been demonstrated within the arterial walls, renal arteries, and psoas muscles of hypertensive persons, even the sodium content of the blood serum and cerebrospinal fluid is higher than normal in such cases (Edwards, 1960).

The relation of salt intake to high blood pressure has also been fully investigated by several workers, with conflicting results. In one series of cases, hypertension was nonexistent in individuals on low salt intakes while it was present in all persons with high sodium intake. Moderate rises of systolic and diastolic pressure have been reported in normotensive persons after the ingestion of 25 to 60 Gm salt (McDonough and Wilhelmi, 1954). A high salt intake has been considered as a cause of hypertension in tropical climates (Schroeder, 1958). Restriction of salt to below 1 Gm/day or of sodium ion to below 200 mg/day may bring about return of blood pressure levels to normal in about 30 per cent of hypertensive patients (Martini and Kaiser, 1954).

According to Freis (1960), salt plays a secondary rather than a primary role in hypertension. Whether disturbance of the salt metabolism is primary and conducive to hypertension or secondary to the renal effects of hypertension, whether a high salt intake is essential for the development of hypertension, and whether salt restriction is indicated routinely in the treatment of high blood pressure are only some of the many unsolved questions of the day, regarding the role of salt in hypertension

Clinical Manifestations ONSET In the great majority of patients with essential hypertension, the disease is discovered either accidentally or during a routine clinical or insurance examination, the condition then being more or less asymptomatic. In some persons, the onset is insidious or gradual, with a few occasional symptoms suggestive of hypertension, such as *headache*, *giddiness*, and *palpitation*. In some, the disease is discovered because of one or another of its possible complications, such as renal or cardiac insufficiency. In a few cases, its manifestation is acute, as in cerebral hemorrhage or thrombosis or myocardial infarction.

CLINICAL PICTURE. The clinical picture of hypertension is variable and heterogeneous, depending on the degree, type, and persistence of the high pressure, the organ or organs preponderately affected, and the patient's own reaction or behavior toward the illness.

Essential hypertension is compatible with a normal and asymptomatic existence for years, the patient remaining completely unaware of its presence In such cases, the onset of symptoms may coincide with the disclosure of the diagnosis to the patient. Certain *premonitory symptoms*, such as migraine headache, repeated nosebleeds, and irritability, are at times experienced by the patient many years before the discovery of the disease proper. Many investigators have felt that essential hypertension is asymptomatic and that most of the symptoms that appear to be produced by it are actually due to iatrogenic or psychoneurotic factors, later complications of the disease, or coincidence with other diseases.

The most common symptoms encountered in essential hypertension may be conveniently grouped into premonitory hypertensive, atherosclerotic, cardiac, renal, neurogenic, psychoneurotic, iatrogenic, and coincidental symptoms

SYMPTOMS. The early symptoms of hypertension include headache, dizziness, vertigo, precordial ache or "fullness," palpitation, excessive fatigue, lassitude, nocturia, polyuria, tightness of scalp, pain in the back of the neck, irritability, blurring of vision, insomnia, tinnitus, emotional instability, dry cough, and lack of concentration In other cases, attention may first be drawn to the ailment because of epistaxis, episodes of coronary thrombosis, cerebrovascular episodes, paroxysmal dyspnea, sudden blindness, mental impairment, vomiting, muscle twitching, generalized convulsions, intermittent claudication, vasomotor phenomena including "dead fingers," joint pains, pares- [illegible] ... tite. The clinical pic-

4. Metabolic
   a. Overeating
   b. Deranged metabolism of proteins, carbohydrates, fats, salt, or purines
5. Neurogenic
   a. Organic lesions of central nervous system
   b. Lesions of autonomic nervous system
6. Psychogenic (psychosomatic)
7. General adaptation syndrome—intensification, protraction, or perversion of the "adaptation syndrome," a protective mechanism against "stresses" such as fatigue, cold, infection, emotion, and intoxication (Selye)
8. Miscellaneous—intestinal disturbances, infection, syphilis, allergy, abuse of tobacco, lead poisoning

There are two ways in which pressor substances may conceivably increase arteriolar tone: (1) normal vascular reaction to excessive amounts of vasoconstrictor or pressor substance, (2) excessive vascular reaction to normal amounts of pressor substance

ETIOLOGIC FACTORS Evidence at hand suggests the participation of several important factors, besides the so-called pressor mechanism, in the genesis of essential hypertension (1) hereditary or genetic factor, (2) constitutional factor, (3) environmental factors, (4) intrinsic sensitization of target organs (the arteriole)

Genetic Factor. An inherited tendency to hypertension is suggested by several studies The familial incidence, studies in twins, and proved inheritance of vascular hyperreactivity to the cold-pressor test (Hines, 1937), support such a theory The predisposition to the disease is probably inherited as a mendelian dominant characteristic (Weitz). According to Ayman (1934), the likelihood of occurrence of hypertension in the offspring is about 3 per cent with normotensive parents, 28 per cent with one parent hypertensive, and 46 per cent with both parents hypertensive

Constitutional Factor The constitutional make-up of the hypertensive male, inclusive of physical, emotional, and mental characteristics, is somewhat typical. He is usually a broad, stockily or squarely built, hypersthenic person of mesomorphic type, emotionally dynamic, ambitious, and aggressive Weiss and Parker (1939), after a somatometric study of 3,000 persons selected at random, were able to demonstrate an unequivocal relationship between blood pressure and thoracic circumference; a lesser degree of correlation was observed between the "height-weight ratio" and blood pressure, the former being inversely proportional to the latter.

Psychopathology. Many workers have been impressed by the association with hypertension of certain personality patterns or traits. The most important of these is an aggressive or explosive temperament, a conflict between hostile impulses and dependent needs, and a tendency to worry over trifles. According to Menninger (1938), beneath a deceptively gentle façade, the hypertensive individual displays a strong undercurrent of fear or hostility based on a threat to his security.[2] Many other investigators have cast doubt on the accuracy or validity of any simple personality profile for hypertension.

Environmental Factors. Dietary factors (overeating), excess of fats or calories in the diet, and emotional traumatic experience may also be important predisposing factors.

The Role of Salt in Hypertension. The role of electrolytes, and particularly of salt or sodium chloride, in the genesis of hypertension has been the subject of considerable debate in recent years Despite innumerable investigations, there is as yet no unanimity of opinion on the subject.

Patients with essential hypertension show augmented urinary salt excretion both in basal condition and under salt load, e.g., after infusion of saline solution and water In comparison with normotensive subjects, hypertensive persons appear to retain sodium and water more readily on a sodium-free diet and excrete more sodium and water under salt load (Hollander and Judson, 1958). On the basis of salt excretion in hypertensive patients, Green and Ellis (1954) recognized two groups of hypertensive persons (1) high salt excreters, probably in the early phase of hypertension, and (2) normal salt excreters, probably in advanced stages of hypertensive disease. Cyclic derangements of sodium chloride exchange and excretion of similar nature were demonstrated in human subjects with hypertension and in animals with experimental hypertension (Wilson, 1953, Taquini, Blaquer, and Taquini, Jr., 1958, Birchall et al., 1953). The increased sodium excretion, or natriuresis, of hypertensive patients under salt load appears to depend not on renal factors (such as impaired tubular resorption of sodium), increased adrenal activity, or modifications of osmotic pressure, but rather on some extrarenal mechanism (Baldwin et al., 1958, Selkurt, 1951; Chinard, 1958). The high excretion of sodium under load is probably related to the level of the raised arterial blood pressure (Hollander and Judson, 1954), and tends to

[2] See Chap 2, this Part. *Editor*

B Arteriosclerotic retinopathy
C Diabetic retinopathy
D Visual disturbances
1. Amaurosis or amblyopia
2. Hemianopsia
3. Scotomas

VII Miscellaneous
A. Gastrointestinal (hematemesis)
B. Respiratory (hemoptysis or cough)
C. Endocrine

Benign and Malignant Phases. The recognition of a *severe or malignant form of essential hypertension* in younger age groups, with acute and rapidly progressive renal insufficiency leading to renal failure, high diastolic pressure, and typical lesions (endarteritis, arteriolar necrosis, and multiple thromboses of small renal arteries), was made possible by Volhard and Fahr (1914). The slowly progressive benign and much more common form of essential *hypertension*, accounting for about 90 per cent of cases, is associated with little or no evidence of renal insufficiency, and was described by Volhard and Fahr as *benign hypertension*

Keith, Wagener, and Kernohan (1928) later presented a classic description of the "syndrome of malignant hypertension" based on the study of 81 cases. After this description it became customary to regard benign and malignant hypertension as clinically *distinct* entities, with different rates of progression, and different incidence of renal involvement, clinical and pathologic manifestations, and prognosis Such a viewpoint cannot be maintained, for several reasons Malignant hypertension may arise at any time during the *course* of an apparently benign or asymptomatic *form of* hypertension, and may even rarely revert to the benign form, either because of treatment or naturally. Benign and malignant *forms of* hypertension may be encountered at *times in* different members of the same family. The pathologic lesion of arteriolosclerosis is common to both the benign and the malignant forms of the disease It is, therefore, imperative to regard the two syndromes as phases of the same disease, rather than as *distinct* clinical entities. In view of the dreadful implication of the word "malignant" to the patient and ...

... ...

The mechanism of the malignant phase remains obscure, in spite of numerous clinicopathologic studies According to many investigators the basic difference between "malignant" and "benign" hypertension is one of *degree* only, the former being no more than an aggravation or acceleration of the disease process, *secondary to persistent and excessive elevation of diastolic pressure*. In conclusion, depending upon the rate of progression of the disease, two main phases of essential hypertension may be recognized.

1 *Benign (nonmalignant or chronic) phase*. This is usually characterized by gradual or insidious onset, long duration extending over 10 to 40 years, slow progression, little or no evidence of renal insufficiency, diastolic level usually below 125 mm Hg, hypertensive retinopathy of grade I, II, or III, and normal blood chemistry. The prognosis is relatively good

2. *Malignant (accelerated, papilledematous, or acute) phase*. This is characterized by acute or subacute onset, rapid *progression, short* course (under 2 years), diastolic level usually over 125 mm Hg (at times 150 *or more*), retinopathy of grade IV with papilledema (*at times, grade III type of fundus*), *early* evidence of azotemia, and renal failure. The kidney has a poor concentrating power, with albuminuria and microscopic hematuria. Present also are anemia, nausea and vomiting, severe headaches, *often convulsions*, rapid and progressive *loss of* vision, tendency to involuntary muscle movements The prognosis is grave, *and early death* may be expected This prognosis may now be modified by treatment. At times, differential diagnosis between the two forms of hypertension is extremely difficult, particularly when grade III retinopathy is associated with evidences of renal dysfunction

Cardiovascular Manifestations. In essential *hypertension*, two major factors act on the heart: (1) *mechanical overload*, due to the increased peripheral resistance (arteriolar vasoconstriction); (2) *inadequate blood supply* (myocardial ischemia), due partly to coronary atherosclerosis and partly to relative ischemia of the hypertrophied myocardial fibers. In hypertensive hypertrophy of the heart, the muscle fibers increase in size but not in number, the fiber-capillary ratio remaining unchanged, the capillaries being *unable* to cope with the demands, there is decreased exchange of oxygen and metabolites. In spite of these influences, the heart is able to carry on, as a rule, for ... of its compensatory

ture of hypertension is greatly influenced by the site, degree, and nature of atherosclerotic complications, the presenting symptom or symptoms being therefore of cardiac, coronary, aortic, arterial, renal, cerebral, musculoskeletal, or ocular origin

Headache. Headache is encountered in the great majority of cases of hypertension, particularly in malignant hypertension. It is recurrent, frequently occipital, tends to occur in the early hours of the morning, and is not necessarily related to the degree, duration, or type of hypertension Headache is relieved at times by sitting up, standing, and moving about; it is frequently improved by hypotensive drugs, is associated in some cases with nausea or vomiting, and is often accompanied by tightness or aching of the neck muscles Usually due to the raised level of arterial pressure, particularly diastolic, the headache of hypertension may also be caused by complication of the hypertension, raised intracranial tension, renal insufficiency, encephalopathy, cerebrovascular lesion, tonic spasm of head and neck muscles (Wolff, 1948), psychogenic or iatrogenic factors, dilatation of carotid artery branches (Wolff, 1948), or true migraine

Dizziness and Vertigo A sudden feeling of unsteadiness or insecurity, or true vertigo, may occur from time to time in essential hypertension, particularly in association with a sudden change of posture or when the patient is taking ganglion-blocking drugs It is usually due to vascular disturbances of the internal ear or eighth nerve Of similar origin are buzzing, ringing, or "sea-shell" noises (*tinnitus*), this complaint, though usually transitory, is often refractory to treatment

Recurrent hemorrhages of varying severity (epistaxis, menorrhagia, metrorrhagia, hematuria, or subjunctival or retinal hemorrhages) may commonly occur in hypertension

PHYSICAL SIGNS The only signs which can be directly attributed to the hypertension are the hard pulse, the abnormal 2d sound in the aortic area, and the *forceful or heaving apex beat*. First described by Traube (1870), the hard pulse of hypertension is like a "taut iron wire," difficult to compress but not necessarily increased in volume or amplitude The loud aortic 2d sound of hypertension, also described by Traube, is frequently associated with a palpable shock or thud and a ringing or metallic quality. Usually attributed to forceful closure of the aortic valve, this sign has some diagnostic value. Unfortunately, it is also present in syphilitic aortitis, aortic atheromatosis, and aneuryism of the aorta. Moreover, the typical aortic 2d sound may be absent if there is associated pulmonary emphysema or obesity. A heaving apex beat, even when normally located, must suggest the possibility of left ventricular hypertrophy secondary to hypertension.

COMPLICATED HYPERTENSION

Essential hypertension, in its early stage, with few or no clinical manifestations, is usually referred to as *uncomplicated* hypertension When clinical symptoms and signs, suggestive of cardiac, aortic, renal, cerebral, or retinal involvement, are present, the hypertension is described as complicated.

COMPLICATIONS OF HYPERTENSION

I Cardiac involvement—left ventricular hypertrophy (compensated phase)
  A Cardiac failure (decompensated phase)
    1 Left ventricular failure
    2 Combined failure
  B Coronary insufficiency
    1 Myocardial infarction
    2 Angina pectoris
    3 Intermediate coronary syndromes
    4 Sudden death
II Aortic involvement
  A Atheroma of aorta
  B Aortic aneurysm
  C Dissecting aneurysm
  D Thrombotic occlusion
III Involvement of peripheral arteries
  A Peripheral arteriosclerosis
  B Peripheral gangrene
  C Thrombotic occlusion
IV Cerebral involvement
  A Hypertensive encephalopathy (spasm or edema)
  B Cerebral thrombosis
  C Cerebral hemorrhage
  D Subarachnoid hemorrhage
  E Cerebral atherosclerosis
  F Cerebrovascular insufficiency
V Renal involvement
  A Benign nephrosclerosis
  B Malignant nephrosclerosis
  C. Functional disturbances
VI Involvement of eyes
  A Hypertensive retinopathy
    1. Grade I—vascular spasm
    2 Grade II—vascular sclerosis
    3 Grade III—exudative phenomena (hemorrhages, exudates, and edema)
    4 Grade IV—papilledema

starting days or weeks before the initial episodes of paroxysmal dyspnea.

The physical signs, although striking and constant in such cases, are often missed. The most important is a triple rhythm (older term, "gallop rhythm"), which is most often presystolic but may be protodiastolic or of the summation type. This is best heard near the apex, and is due to the presence of an extra sound during diastole. Once considered of ominous significance and pathognomonic of left ventricular failure, triple rhythm is compatible with fairly long survival, may persist in spite of additional right ventricular failure, and may disappear with therapy.[4] The other signs of left ventricular failure are an outward and downward displacement of the apex beat (at times, in the anterior axillary line, in the 6th and left interspace), with increased amplitude and extent but relative decrease of force (less forceful than during the previous stage of left ventricular hypertrophy), indicating dilatation of the left ventricle, increased loudness of the 2d sound over the pulmonary area (the pulmonary 2d sound becomes as loud as the aortic sound or even louder); moist rales over the lung bases (at times throughout both lungs), pulsus alternans (with regular alternation of strong and weak beats at the radial pulse), best appreciated with a sphygmanometer (Gallavardin's sign), a sudden doubling of the sounds being detectable during deflation of the cuff.[4]

Combined Failure Insufficiency of both ventricles (left- plus right-sided failure) may occur in hypertension, usually after a phase of left ventricular failure of varying duration, provided the patient has not already succumbed to other major complications, such as coronary thrombosis, renal failure, or cerebral hemorrhage.

The onset of right ventricular failure is usually manifested by *signs of systemic venous stasis*, including dependent edema (usually at the ankles or pretibial in ambulatory cases and sacral in recumbent cases), hepatomegaly, and engorgement of the cervical veins. Evidence of enlargement of the heart to the right and left, and transudates in the serous cavities (hydrothorax or ascites) become apparent. *Ectopic rhythms* are common (premature beats, atrial fibrillation). It is interesting that occasionally even when cyanosis develops, paradoxical improvement in the severity of dyspnea occurs (tricuspid insufficiency). In severe cases, and particularly in elderly subjects, *periodic respiration* of the Cheyne-Stokes type, a soft, early diastolic aortic murmur, restlessness, and delirium may further complicate the picture.

X-ray may disclose a huge heart, of a triangular or globular cardiac configuration, with diminished pulsations. The *electrocardiogram* may show low voltage, sinus tachycardia, various types of arrhythmias, and evidence of both right and left strain, with or without evidences of hypertrophy.

Bernheim's Syndrome. In a few cases of hypertension with left ventricular enlargement, the clinical picture may be dominated, paradoxically enough, by right ventricular, rather than left ventricular, failure. Evidence of systemic venous stasis may predominate over that of pulmonary congestion. This syndrome was described by Bernheim (1910) and attributed to massive hypertrophy and rigidity of the interventricular septum, reducing right ventricular filling. However, the very existence of this syndrome is denied by several contemporary authors.[5]

Coronary Thrombosis In some patients with hypertension, the clinical picture may be dominated or initiated by myocardial infarction.

Exertional Precordial Pain (Angina of Effort). In many cases of hypertension, with or without evidences of ventricular hypertrophy or strain, precordial pain may disturb the patient long before the advent of dyspnea. Typically paroxysmal and related to physical exertion, excitement, or overeating, the pain or sensation of constriction starts retrosternally, usually radiates to the left arm (at times, down the right arm or both arms, or to the left elbow, lower jaw, epigastrium, or back), attains its peak within a matter of seconds or minutes, lasts usually for 1 to 20 min, and usually responds promptly to rest or nitrites. Transient depressions of the S-T segment, with diphasic or inverted T wave in several leads

[4] The description and significance of triple rhythms, as well as alternans, may be found in Part 5, Chap 4. *Editor*.

[5] Recent reports have shown the possibility of either pulmonic or aortic stenosis as a result of hypertrophy of the ventricular septum. On the other hand, no single case of Bernheim's syndrome has been confirmed, so far, by catheterization. *Editor*.

mechanisms, and the patient remains asymptomatic. In some cases, however, cardiac manifestations appear early, dominating the clinical picture.

CARDIAC MANIFESTATIONS The heart may be affected in the following ways:

I. Left ventricular hypertrophy (compensated heart)
II. Cardiac failure
   A. Left ventricular failure
   B. Combined (left and right) failure
   C. Bernheim's syndrome (or paradoxical failure)
III. Coronary insufficiency
   A. Coronary thrombosis (followed by myocardial infarction)
   B. Exertional precordial pain (older term, "angina of effort")
   C. Intermediate coronary syndrome
   D. Sudden death
IV. Terminal pericarditis (final stage of malignant hypertension)—very rare
V. Valvular involvement—rare

Left Ventricular Hypertrophy The earliest and commonest effect of hypertension on the heart is hypertrophy of the left ventricle. It is the result of the increased work of the heart against the increased peripheral resistance. It is completely asymptomatic.

This ventricular hypertrophy is usually accompanied by little or no dilatation (concentric hypertrophy). Therefore, the size of the heart may appear normal on physical examination; the apical thrust is either in its normal place or is but slightly displaced downwards and (at times) outwards. The most dependable sign of left ventricular hypertrophy is a forceful or heaving apex beat, that lifts the palpating finger with force; the amplitude of apical pulsation is usually normal, unless there is cardiac dilatation or thyrotoxicosis. There may be increased retromanubrial cardiac dullness on percussion, a loud, booming, prolonged (and at times split) 1st heart sound at the apex, a loud, sharp, and metallic 2d sound at the aortic area, a systolic apical murmur (caused by dilatation of the AV ring or mitral valvular sclerosis), a systolic murmur at the aortic area (caused by dilatation of the aorta or a sclerotic aortic valve), and, at times, a characteristic, frequently transitory, diastolic murmur (due to functional aortic regurgitation) over the basal areas of the heart.

X-ray may reveal a boot-shaped, transversely placed cardiac silhouette, with increased convexity of the left lower border (best seen during deep inspiration), and a rounded or blunt apex; the transverse diameter of the heart may be normal.

The most common and important *electrocardiographic findings* are left axis deviation, increased voltage of the QRS complex (large S waves in V_1 and V_2 and large R waves in V_5 to V_6), increased duration of the QRS complex (over 0.11 sec), depression of the S-T segment (over 0.5 mm), and inversion or depression of the T wave in lead I (at times also in lead II), AVL, V_5 *to* V_6. $R_1 + S_3$ is usually over 20 mm, and $SV_1 + RV_5$ or V_6 is over 28 mm. The characteristic S-T and T-wave changes of leads I and II have been variously attributed to ischemia of the left ventricle, change in position of the heart, and rotation of the heart caused by left ventricular hypertrophy.

After a variable period of time (weeks to years) the compensatory phase of left ventricular hypertrophy may change to isolated *failure of the left ventricle* (Gallavardin). The development of failure may be insidious or acute, and triggered by a variety of factors, such as myocardial ischemia, acute respiratory infection, sudden rise of blood pressure caused by excitement, anger, exposure to cold, severe exertion, nightmares, emphysema, or a valvular lesion.

Left Ventricular Failure The presenting symptom in most cases of early left heart failure is *dyspnea*. This may be acute and nocturnal (paroxysmal nocturnal dyspnea; older term—"cardiac asthma"), arising suddenly in the early hours of the night, with air hunger, orthopnea, restlessness, and cough. It may also develop more gradually, as exertional dyspnea. In more advanced cases, the dyspnea may become continuous. Paroxysmal nocturnal dyspnea may be complicated by acute pulmonary edema, with expectoration of pink, frothy sputum.[3] The intensity, duration, nature, and frequency of such attacks vary from patient to patient. Careful questioning may elicit a history of prodromal or premonitory symptoms of dry nocturnal cough, nocturia, oliguria, insomnia, exertional fatigue or dyspnea, and decreasing exercise tolerance,

[3] Paroxysmal pulmonary edema is discussed in detail in Part 18. *Editor.*

retinal vessels, retina, and optic disk, and presents a wide variety of ophthalmoscopic appearances

The classificaton of hypertensive retinopathy into [illegible] grades or degrees of increasing severity, [illegible] forward [illegible] states [illegible] tic and prognostic importance regarding hypertension.

Grade I (vascular spasm): narrowing of smaller arterioles with localized constrictions and increased tortuosity

Grade II (vascular sclerosis): narrowing of arteries, with irregular, waistlike constrictions and increased tortuosity, exaggeration of "light reflex" through thickening of arterial walls, "copper wire" appearance of arteries when filled with blood, and "silver wire" appearance when relatively empty, full veins or distended and tortuous ones; altered "artery to vein diameter ratio", arteriovenous compressions (Gunn's phenomenon), resulting in nicking of veins, invisibility of underlying veins, and *U-shaped or S-shaped venous curvatures*

Grade III (hypertensive neuroretinitis or exudative retinitis), same as grade II, but with additional features, soft, "cotton-wool exudates" or patches with fluffy margins, multiple or single flame-shaped or striate hemorrhages, retinal edema, with haziness of outlines of retinal vessels and (occasionally) blurring of disk margin

Grade IV (papilledematous retinitis) same as grade III, but with additional features papilledema, with the optic disk clearly raised above the level of the retina and shallowness or absence of the physiologic cup Grade IV retinitis is usually considered diagnostic of the malignant phase of hypertension

In Leatham's opinion, a presumptive diagnosis of hypertension is justified in the presence of one or more of the following ophthalmoscopic criteria (1) irregularity of lumen of two or more arterioles; (2) generalized narrowing of arterioles, with arteriole-venule diameter ratio of 1:2, and (3) arteriovenous nicking, pallor of arteriolar column, and broad or bright "light streaking."

NATURAL HISTORY OF HYPERTENSION

Increasing familiarity with the disease suggests that evolution or development of hypertension is a long process, probably beginning at birth with a predisposition to the disease and developing, stage by stage, as outlined below

1. Hereditary (constitutional or familial) tendency (potential hypertension)
2. Prehypertensive phase (latent hypertension)
3. Intermittent (phasic, episodic, or neurogenic) hypertension
4. Established (sustained, persistent, or continuous) hypertension, uncomplicated
5. Established hypertension, complicated–associated with cardiovascular, renal, cerebral, or other complications, or with the malignant syndrome
6. Death (from cardiovascular, cerebrovascular, renal, or coincidental causes)

Prehypertensive Phase. This may be detectable years before the actual onset of high blood pressure, by observation of the following features: (1) high levels of blood pressure during states of mental strain, e g , during insurance examination; (2) occasional pressure readings in the upper ranges of normal or well above average or mean levels, (3) hyperreaction or increased reactivity to pressor stimuli. The latter may be of the nature of reflex stimulation, e g , cold-pressor test (Hines and Brown, 1935), muscle ischemia test (Alam and Smirk, 1938), or Valsalva maneuver (Finnerty and Freis, 1950); chemical stimulation, e g., carbon dioxide inhalation (Raab, 1953) or breath-holding test (Ayman and Goldshine, 1939); pharmacologic stimulation (after blocking the control mechanism with hexamethonium) with norepinephrine, angiotension, or S-methyl-iso-thiourea (Doyle and Black, 1955); or psychic stimulation, e.g., emotional stimulation through tense interview or mental tension.

Of the various tests for vascular responsiveness or reactivity, the most useful is the *cold-pressor test* After the basal pressure level has been determined, the patient's hand is immersed in ice-cold water up to the wrist for 1 min. The blood pressure is measured in the opposite arm, every ½ min for 1 min and, later, every 2 min, until the basal level is regained. A pressure reaction below 20/15 is called "normal hyporeaction", over 20/15, "normal hyperreaction"; and over 30/20 or 40/30, "abnormal hyperreaction," suggesting hypertension in its prehypertensive or latent phase.

Intermittent Hypertension. In the functional or spastic stage of hypertension, elevations of blood pressure are usually phasic or episodal, lasting for minutes, hours, or days and alternating with phases of normotension. Detection of hypertension in this stage is important, because of a good response to treatment.

of the electrocardiogram, are common during an attack of pain, although the electrocardiogram may be completely normal between attacks. Angina pectoris in a hypertensive patient, as in a normotensive patient, may be frequently associated with a transitory rise in blood pressure. Precordial pain of hypertension does not always indicate coronary atherosclerosis, since typical pain may be due to inadequate blood supply (coronary insufficiency) resulting from myocardial hypertrophy and increased cardiac work. However, moderate coronary arteriosclerosis is usually present.

Intermediate Coronary Syndrome. Clinically intermediate between angina pectoris and coronary occlusion is a coronary syndrome, neglected in the past, that has been variously designated as coronary failure (Blumgart et al., 1941), acute coronary insufficiency (Master et al., 1947), intermediate coronary syndrome (Graybiel, Vakil), and prethrombotic syndrome (Vakil, 1951). The pain is then typically retrosternal but lasts for hours instead of minutes, and is not associated with fever, leucocytosis, high sedimentation rate, and increase of transaminase, as in myocardial infarction.

Valvular Lesions. Involvement of the mitral or aortic valves may, at times, complicate the clinical picture of hypertension. The cause of the lesion may be rheumatic, syphilitic, or atherosclerotic. *Calcific aortic stenosis* is probably the more common coexisting lesion. The differentiation between obstructing aortic stenosis, nonobstructing aortic stenosis, and relative aortic stenosis must then be made.

Arterial Manifestations. Besides involving the small arterial vessels supplying blood to vital organs, such as the heart, kidneys, and brain, hypertension may also affect the aorta and the peripheral arteries of the extremities.

Aortic involvement, in hypertension, usually consists of atherosclerosis, causing elongation and dilatation of the aorta. Usually symptomless, except in cases of massive aneurysm or embolization, aortic involvement may be suspected on the basis of certain physical signs: visible and palpable pulsation of the aortic arch, above and behind the manubrium, visible and palpable arterial pulsation in the right lower cervical region (Rowntree's sign), dullness over the manubrium, loud and ringing 2d sound, moderately loud systolic murmur at the aortic area, and a high pulse pressure.

Cerebral Manifestations. Apart from nonspecific symptoms, such as headaches, fatigue, throbbing sensations, and vertigo, certain characteristic symptoms may suggest cerebral involvement. The following *cerebral syndromes* may occur:

I Hypertensive encephalopathy
  A Vasospasm with cerebral hypoxia
  B Cerebral edema
  C. Minute vascular accidents
II Cerebrovascular accidents
  A Cerebral thrombosis
  B Cerebral hemorrhage
III Cerebral atherosclerosis
  A Atherosclerotic Parkinsonism
  B Pseudobulbar palsy
  C Mental degeneration
IV Cerebral symptoms of uremic origin

HYPERTENSIVE ENCEPHALOPATHY. Attacks of hypertensive encephalopathy were described for the first time by Fishberg (1928). Usually transitory, these attacks, caused by cerebral angiospasm, may result in a variety of disturbances of cerebral function: sudden and transitory loss of consciousness, aphasia, convulsions, paresis or paralysis, sensory disturbances, amaurosis, and disorientation. Particularly frequent during the malignant phase of hypertension, these evanescent episodes may be due to cerebral hypoxia, cerebral edema (secondary to vasoconstriction), or minute thrombosis involving silent areas of the brain. A sudden and severe drop of blood pressure, secondary to ganglion-blocking agents, may be responsible for hypoxia if certain cerebral vessels are rigid and narrow.

Hypertensive Retinopathy. Observed ophthalmoscopically, for the first time by Heymann (1856), and lucidly described under the designation of *albuminuric retinitis* by Liebreich, the retinal manifestations of hypertension include three main types of retinopathy: hypertensive, arteriosclerotic, and diabetic.

The characteristic retinopathy of hypertension (hypertensive retinopathy), which is common to most forms of hypertension and is frequently associated with a high level of diastolic blood pressure (as in malignant hypertension), involves, to a variable extent, the

in the literature of the past. In spite of possible serious complications, such as congestive failure and cerebral hemorrhage, which may kill some patients and cripple others, the average life span of an untreated hypertensive patient is about 20 years, with a wide range of from several hours to over 40 years. Essential hypertension frequently proves fatal during the fifth decade of life, and reduces the life span by about 10 years (Weitz and Fishberg) Depending on the method of selection of cases and on the nature of the survey employed, the prognosis of hypertension has been outlined in different manner by different observers.

Benign essential hypertension is, as a rule, a slowly progressive disease, compatible with many years of comparatively comfortable existence. In Riseman's opinion, it is "not conducive to longevity but is compatible with longevity."

Causes of Death. The major causes of death and invalidism in hypertension are congestive failure (50 per cent), coronary heart disease (15 per cent), cerebrovascular accidents (15 per cent), uremia (8 per cent), and coincidental or unrelated ailments (12 per cent). Two-thirds of all deaths are due to involvement of the heart or its arteries.

Cure or Recovery. A genuine cure or disappearance of high blood pressure is seldom, if ever, possible in an established case of essential hypertension. A transitory or persistent drop of pressure to normal may, however, occur through a complication, such as coronary thrombosis, peripheral failure, or shock (as in peritonitis or following a cerebrovascular attack; through general debility, malnutrition, or cachexia, or as the result of medical or surgical treatment. A genuine recovery also appears possible during the earlier prehypertensive and intermittent phases of essential hypertension, when the functional vascular disturbance is apparently still reversible.

Data of Prognostic Significance. The complications and sequelae that may result from essential hypertension or its major complication, atherosclerosis, are many Prognosis is therefore extremely difficult. Data on the following topics are of some prognostic value and must therefore be carefully evaluated in all cases.

AGE. The outlook is, as a rule, better in elderly persons than in the young. The incidence of malignant hypertension is higher in younger age groups.

SEX. Because of the lower incidence of coronary disease and malignant hypertension in women, the outlook is better in women than in men, death expectancy being only about half that of males.

LEVEL OF BLOOD PRESSURE. The outlook depends, to some extent, on the degree of elevation of diastolic and systolic pressures, particularly the former. For this purpose, basal readings of pressure are far more dependable than casual. The mortality rate and incidence of complications increase proportionally with the increase of blood pressure up to about 210/120, above this level, there is a steep rise, mainly because of the high incidence of cerebral hemorrhage and malignant hypertension.

FIXITY OF BLOOD PRESSURE. The prognosis is better in the labile form of hypertension, even if the pressure level is high, than in the fixed or refractory form. The former type is also more amenable to therapeutic measures

TYPE OF HYPERTENSION. Diastolic hypertension, as a rule, is far more serious than systolic hypertension, which may be the result of aortic atherosclerosis.

SYMPTOMS. The mortality rate of hypertensive patients presenting symptoms is about five times that of persons with latent or asymptomatic hypertension (Frant and Coren, 1950).

RETINAL GRADING According to Wagener and Keith (1939), the 5-year mortality rate of hypertensive patients is 30 per cent for grade I, 40 per cent for grade II, 80 per cent for grade III, and 99 per cent for grade IV, the average duration of life for those with the malignant or papilledematous form of hypertension being only about 1 year. True papilledema is therefore a sign of ominous significance.

OBESITY. Excessive body weight tends to increase the mortality rate in hypertension by predisposing to coronary heart disease.

RENAL FUNCTION. Impaired concentrating ability of the kidney and high nitrogen retention in the blood indicate a bad prognosis, unless accounted for by prerenal azotemia or prostatic obstruction. Among urinary abnormalities, massive albuminuria and excess of granular casts are particularly significant and often indicate a poor outlook

DIAGNOSIS

Diagnosis of essential hypertension implies the demonstration of persistently elevated diastolic and systolic blood pressure levels, in the absence of all known causes of hypertension, such as renal, endocrine, and cerebral disease.

Diagnostic difficulties may arise in cases of early, borderline, intermittent, or latent hypertension. Occasionally high blood pressure, particularly during medical, insurance, or military examinations or under conditions of sustained emotional stress (e.g., during combat duty or states of psychosis), may be either an evanescent phenomenon of no significance or a sign premonitory of true hypertension. Serial observations of basal blood pressure readings may prove necessary in such cases for establishing the final diagnosis.

The blood pressure, even in severe hypertension, may drop to normal after a major complication, such as myocardial infarction or cerebral thrombosis The hypertensive disease may then be missed unless it was known to have been present prior to the catastrophic illness A persistently high level of the diastolic pressure, in spite of a drop of mean pressure, may reveal the preexisting condition.

Differential diagnosis of malignant from benign hypertension may prove difficult when advanced retinal changes, urinary abnormalities, or very high levels of blood pressure are present. Mere blurring of the margins of the optic disk, through retinal edema, as in grade III hypertension, may be mistaken for true papilledema, while the finding of albumin and casts in the urine may prejudice the examiner in favor of the malignant syndrome

Systolic hypertension, from coarctation of the aorta, senile atheromatosis, or thyrotoxicosis, may be incorrectly diagnosed and the patient may be treated for essential hypertension if no attention is paid to the level of diastolic pressure.

Since success or failure of treatment depends to a great extent on a correct appraisal of the nature and type of the high blood pressure state, a systematic method of interrogation and investigation, such as the following, is essential in every case of suspected hypertension.

I. Interrogation
   - *A.* Routine: familial incidence, age, sex, occupation
   - *B.* Special: onset; duration; progress, aggravating and relieving factors; associated symptoms; presence of complications

II. Routine examination
   - *A.* Blood pressure: brachial pressure (right and left sides); postural effects (pressure readings in recumbent, sitting, and standing postures), femoral pressure; pulse pressure; basal and supplemental pressures; Gallavardin's sign (detection of pulsus alternans by sphygmomanometry).
   - *B.* Pulse: rate, rhythm, force, tension, appearance, character, inequality, condition of the arterial wall; pulsus alternans.
   - *C.* Routine system review (particularly cardiovascular system). Special attention should be paid to the following: apex thrust (site, intensity, character, extent); pulsatory phenomena at the base of the heart; heart sounds (comparative intensity of aortic and pulmonary 2d sounds), triple rhythm; rales and rhonchi; edema; cyanosis; hepatomegaly; serous effusions, Rowntree's sign (pulsation in right lower cervical region).

III. Routine investigations
   - *A.* Blood tests: routine blood count; erythrocyte sedimentation rate, serologic tests, blood urea and nonprotein nitrogen; fasting blood sugar; blood cholesterol, serum sodium, potassium, and chloride; carbon dioxide combining power.
   - *B* Urine tests. protein (albumin); specific gravity, sugar; sediment (cells, casts, red blood cells, etc.); color; polyuria, oliguria, nocturia, phenol sulfonephthalein test
   - *C* Electrocardiogram: axis deviation, voltage and duration of QRS complex, T-wave flattening or inversion, S-T changes; other abnormalities.
   - *D.* Fluoroscopy size of cardiac silhouette; border convexity of left ventricle, pulsations, aorta, hilar shadows; lung fields, fluoroscopy in RAO and LAO positions, skiagrams of chest, roentgenograms of abdomen, intravenous pyelography; x-rays after perirenal insufflation.

IV Special investigations
   - *A* For essential hypertension. circulation time (arm-to-tongue time; arm-to-lung time), cold-pressor and other pressor tests, sedation test (Amytal)
   - *B* For secondary forms of hypertension (discussed below).

PROGNOSIS

The prognosis of the average case of essential hypertension is not so gloomy as portrayed

- III. Neurogenic
  - *A* Cerebral
    1. Raised intracranial pressure
    2. Fracture of the skull
    3. Intracranial tumor
    4. Concussion
    5. Encephalitis
    6. Epilepsy
    7. Lead encephalopathy
    8. Purulent meningitis
    9. Diencephalic syndrome
  - *B* Bulbar
    1. Bulbar poliomyelitis
    2. Bulbar palsy
  - *C.* Spinal
    1. Transverse myelitis
    2. Transection of cord
    3. Cervical or upper dorsal lesions
    4. Tabes dorsalis
  - *D.* Peripheral
    1. Polyneuritis
    2. [illegible]
- IV. [illegible]
    1. Coarctation of aorta
    2. Arteriovenous fistula
    3. Aortic regurgitation
    4. Senile atherosclerosis
    5. Congestive heart failure
- V. Psychogenic
- VI Dietetic
- VII Poisoning (endogenous or exogenous)
  - *A* [illegible]
- [illegible]
  - *A.* Gaisboeck's syndrome (polycythemia with hypertension)
  - *B.* Beriberi
  - *C.* Pink disease
  - *D* Postamputational
  - *E* Severe traumatic lesions
  - *F* Hemo- or myoglobinuria
  - *G* Emphysema

The above list of causes of secondary hyper*tension* is by no means final or complete. With the discovery of further causes of hyperten*sion*, more and more entities are likely to be added to the list in the near future

RENAL HYPERTENSION

The association between Bright's disease and hypertension has been known for many years. The frequent *relationship* of hypertension with pyelonephritis or hydronephrosis, on the other hand, has been established more recently. The fact that hypertension may be associated with bilateral or unilateral kidney disease has important diagnostic and therapeutic implications.

The high incidence and great variety of renal lesions demonstrable in cases of hypertension; the experimental production of hypertension by the clamping of renal arteries of dogs (Goldblatt et al., 1934); and the possible abolition of the hypertensive state through removal of a diseased kidney stressed the important relationship between the kidneys and high blood pressure. Following the experiments of Goldblatt and his associates, it was suggested that some cases of essential hypertension might be of renal origin, being caused by excessive elaboration of pressor substances by the ischemic kidneys. Such a viewpoint is no longer tenable in the light of more recent work. Present opinion, however, does ascribe a role of importance to the kidney in 10 to 15 per cent of cases (renal hypertension), in which disease of one kidney, or of both, bears a definite causal relationship to the hypertension

The actual role of *unilateral renal disease* in hypertension is difficult to establish for several reasons. (1) The association between the two conditions may be coincidental, the hypertension being of the essential, rather than the renal, type. (2) Proved renal hypertension, when of long duration, may fail to respond to removal of the diseased kidney. (3) A high level of pressure, recorded before nephrectomy, may be physiologic or psycho*genic rather than* caused by specific lesions. (4) The hypotensive response to nephrectomy does not necessarily prove a renal origin of the hypertension, since a transitory drop of blood pressure may accompany any form of major surgery. Only when a persistent drop of both diastolic and systolic blood pressure to normal level can be demonstrated after removal of an obviously damaged kidney, can the case be regarded as one of hypertension. Renal hypertension, although usually associated with advanced disease of the kidney, may occur early in the course of renal disease, if associated with vascular spasm or sclerosis.

Unilateral renal disease with renal hypertension may be of one of two types. (1) vascular, with obstruction of the renal artery from atherosclerosis, thrombosis, embolism, aneurysm, adhesion, or pressure by tumor or cyst, or because of a congenital anomaly (absence of renal artery or ectopic kidney); (2) parenchymal, in cases of unilateral pyelonephritis, hydronephrosis, renal tumor, tuberculous kidney, renal calculus, or perirenal hematoma.

CARDIAC FAILURE. The presence or absence of heart failure and its degree and type are of utmost importance. Pulmonary edema, paroxysmal nocturnal dyspnea, gallop rhythm, alternans, electrocardiographic evidence of myocardial damage, and refractoriness to treatment indicate a guarded prognosis. When several of these conditions are present, prognosis is definitely worse.

CORONARY INVOLVEMENT A history of episodes of precordial pain or myocardial infarction makes the outlook grave and uncertain, sudden death or further infections being possible during the subsequent course of the disease.

DIABETES. Diabetes predisposes to arteriosclerosis and nephrosclerosis; episodes of hyperglycemia, hypoglycemia, or coma may occur; early occurrence of coronary or cerebral infarcts is not unusual. Therefore, the prognosis for diabetic patients is usually worse.

SIZE OF HEART. Except in coronary disease (in which the outlook may be poor despite a normal heart size), the death rate in hypertension is roughly proportional to the degree of enlargement of the heart.

CEREBROVASCULAR ACCIDENTS Cerebral hemorrhage usually proves fatal within a few days; cerebral thrombosis tends to shorten the life span of hypertensive patients by several years.

TREATMENT. Early, appropriate, and intensive therapy, particularly for a cooperative patient, may affect the prognosis appreciably, especially when the essential hypertension is benign. Even in malignant hypertension, most of the ominous signs may disappear following therapy.

SECONDARY FORMS OF HYPERTENSION

Diastolic, or true, hypertension may be either *primary* (essential), with an obscure etiology (as in 80 to 90 per cent of cases), or *secondary* (symptomatic), with some demonstrable cause (as in 10 to 20 per cent).

Classification of Types of Secondary Hypertension

I. Renal or nephrogenic
- *A*. Affections of renal parenchyma
  1. Acute glomerulonephritis
  2. Chronic glomerulonephritis
  3. Chronic pyelonephritis
  4. Hydronephrosis
  5. Polycystic disease
  6. Diabetic glomerulosclerosis
  7. Renal calculi
  8. Infarction of kidney
  9. Renal tumor
  10. Hypernephroma
  11. Amyloidosis
  12. Scarring or trauma
  13. Radiation nephritis
  14. Ectopic kidney
  15. Hypogenesis
  16. Dystopia
  17. Nephrocalcinosis
  18. Necrotizing nephrosis
- *B* Affections of main renal arteries
  1. Atherosclerotic plaques
  2. Aneurysm
  3. Dissecting aneurysm
  4. Thrombosis
  5. Compression by tumor
- *C*. Affections of small renal vessels
  1. Polyarteritis nodosa
  2. Thromboangiitis obliterans
  3. Dermatomyositis
  4. Scleroderma
  5. Disseminated lupus erythematosus
  6. Embolic nephritis
  7. Lead poisoning
- *D* Affections of ureter and pelvis
  1. Calculus obstruction
  2. Kinking of ureter
  3. Pressure on ureter
  4. Pyelitis
- *E* Perirenal affections
  1. Perinephric abscess
  2. Tumor
  3. Hematoma
  4. Retroperitoneal affection
  5. Wilms's tumor

II Endocrine
- *A* Adrenal
  1. Hypercorticism (adrenocortical hyperfunction)
     - *a* Cushing's syndrome
     - *b* Adrenogenital syndrome
     - *c* Primary aldosteronism (Conn's syndrome)
     - *d* [illegible]
  2. [illegible] ...toma)
- *B* Pituitary
  1. Cushing's disease (basophil adenoma or hyperplasia)
  2. Eosinophil adenoma (rare)
  3. Chromophobe adenoma (rare)
- *C*. Thyroid
  1. Thyrotoxicosis (hyperthyroidism)
  2. Myxedema (hypothyroidism)
- *D* Ovarian
  1. Climacteric (menopausal)
  2. Arrhenoblastoma
  3. Toxemia of pregnancy
- *E* Parathyroid (rare): primary hyperparathyroidism (with nephrocalcinosis)

CHRONIC PYELONEPHRITIS. The importance of chronic *pyelonephritis* as a cause of renal hypertension, and its high incidence, have been recognized only recently. The condition may be unilateral or bilateral, is common in youthful subjects, particularly women, may follow acute pyelonephritic attacks or recurrent urinary infections, instrumental study of the bladder, urologic obstruction, impaction of renal calculus, enlarged prostate, septic fever, general debility, severe anemia, or neurogenic bladder. The *infection of the kidney* (usually bacterial) is of either the hematogenous (via the blood stream) or the ascending type (via the ureter). It is characterized by a gross pyuria with a massive quantity of pus in the urine, microscopic or frank hematuria, casts, and bacteria; low specific gravity of the urine, high blood urea, and other evidence of renal insufficiency Hypertension, which is a frequent complication, being twice as common in *patients with chronic pyelonephritis* as in normal controls, is usually severe, rapidly progressive, has a tendency to become malignant, and is often associated with encephalopathy, weakness, emaciation, backache, unexplained pyrexia, and facial puffiness Intravenous pyelography, by disclosing characteristic constriction, flattening, distortion, or dilatation of the pelvis or calyces, with shrinkage of one or both renal shadows, helps to establish the final diagnosis

DIABETIC NEPHROSCLEROSIS (KIMMELSTIEL-WILSON SYNDROME). First described by Kimmelstiel and Wilson (1936), diabetic nephrosclerosis is characterized clinically by the presence of diabetes (the causative factor), hypertension, massive proteinuria, nephrotic edema, diabetic retinopathy, arteriosclerosis, and renal insufficiency or uremia. Pathologically, the diagnostic lesion is a nodular or diffuse hyalinization of the glomerular tufts of the kidney. Irrespective of treatment, the course is invariably downhill, with death from uremia or congestive cardiac failure supervening in about 3 years.

ENDOCRINE HYPERTENSION

Abnormally high arterial blood pressure is a manifestation of several endocrine disorders, particularly those affecting the adrenal glands (adrenal hypertension). However, the exact role of endocrine factors *in the genesis* of hypertension has not as yet been elucidated.

Adrenal Hypercorticism. CUSHING'S SYNDROME. This syndrome is caused by overactivity of the adrenal cortex, or *is secondary to* adrenocortical tumor, bilateral cortical hyperplasia, basophil adenoma of the pituitary gland (Cushing's disease), hypothalamic disease, thymoma, or ovarian tumor. Cushing's syndrome is characterized by obesity (90 to 100 per cent of cases), hypertension (80 to 90 per cent), generalized edema, purple *striae atrophicae* over the abdomen, amenorrhea, virilism, plethoric appearance of the face, kyphosis, weakness, osteoporosis of bones, polycythemia, tendency to purpura, and mental symptoms.

Characteristic alterations of the serum electrolytes, including low blood potassium and chloride, normal sodium, and high carbon dioxide; abnormalities of protein, fat, and carbohydrate metabolism; disturbances of androgen-estrogen balance, and normal 17-ketosteroid with raised 11-oxysteroid and 17-hydroxycorticoid contents of blood and urine, confirm the clinical diagnosis The urine does not show a persistently alkaline reaction or a low and fixed specific gravity, as it does in primary aldosteronism.

In pituitary basophilism (Cushing's disease), excess liberation of corticotropin from the anterior lobe of the pituitary brings about adrenocortical hyperfunction with excessive production of adrenocorticotropic hormone (ACTH).

When diabetes and (more rarely) gynecomastia are associated with Cushing's syndrome, the condition is referred to as the "Achard-Thiers syndrome."

PRIMARY ALDOSTERONISM (CONN'S SYNDROME). Aldosterone, a steroid or mineralocorticoid, with potent sodium-retaining activity and a formula of 18-oxycorticosterone, has been isolated from the adrenal cortex. Conn (1955) described a clinical syndrome caused by excessive secretion of aldosterone by the adrenal cortex, and characterized by hypertension, recurrent episodes of muscle weakness, tetany, polyuria, polydipsia, paresthesias, and absence of edema. Numerous cases of Conn's syndrome, secondary to adrenocortical adenoma, carcinoma, or hyperplasia, have been reported. Other characteristics of Conn's syndrome are a high blood pH or alkalosis, high carbon dioxide content of blood, *low serum* potassium (hypokalemia), low serum chloride (hypochloremia), normal or increased serum

Diagnosis. In most cases of renal hypertension, there is a history of episodes of urinary infection, hematuria, puffiness of the face, or generalized edema. Renal involvement in hypertension may also be suggested by the age of the patient (more common in young subjects), fairly acute onset, febrile and rapidly progressive course, negative family history of hypertension, pallor, urinary abnormalities, altered blood chemistry, and abnormal pyelograms

SPECIAL TESTS FOR RENAL HYPERTENSION

1. Blood chemistry
   - *a* Serum proteins (total protein, albumin, globulin)
   - *b* Blood creatinine
   - *c* Calcium and phosphorus content of plasma
   - *d* Alkaline phosphatase
   - *e.* Blood uric acid
   - *f.* Lupus erythematosus cell preparation
2. Excretory tests
   - *a.* Creatinine clearance test
   - *b* Congo red excretion test
   - *c.* Excretion of sodium and water
3. Urinary tests
   - *a.* Urine culture
   - *b* Counts of casts and cells
   - *c.* Bence-Jones protein
4. Radiologic tests
   - *a.* Intravenous pyelogram
   - *b.* Retrograde pyelogram
   - *c.* Radioactive Diodrast
   - *d.* Renal angiogram
5. Biopsies
   - *a.* Renal biopsy
   - *b.* Skin and muscle biopsies
6. Tests for hypertension of unilateral kidney origin

Ingenious tests have been devised for facilitating the diagnosis of hypertension of unilateral renal origin, a type of hypertension frequently amenable to nephrectomy.

HOWARD'S TEST. Based on the assumption that in unilateral kidney disease there is usually some degree of obstruction of the renal artery or a major branch, causing renal ischemia, this test depends on a differential excretion of sodium and water from the kidney. It may be positive even with a normal pyelogram.

The patient, who is on a normal diet for 3 to 4 days, is given 200 ml water to drink every 15 min for 1 hr Urine is obtained simultaneously from each kidney through separate catheters. The test ends when 50 ml urine is obtained from any one kidney. If the volume of urine is reduced by 60 per cent or more in one kidney as compared with the other, and sodium excretion by 16 per cent or more, the test is positive, and nephrectomy is a suitable means of therapy.

This test is helpful for hypertensive patients with one-sided kidney disease, as well as for rapidly progressive or refractory forms of hypertension. A high blood urea nitrogen without dehydration, being evidence of advanced bilateral disease, rules out the test.

WINTER'S RADIOISOTOPE TRACER TEST. Following an intravenous injection of iodine^{131}-labeled Diodrast, the rates of accumulation and disappearance in the kidney areas of the radioisotope are estimated by means of external monitors This so-called *radioactive renogram test* represents a rapid form of screening, useful for selection of patients for nephrectomy.

Special Forms of Nephrogenic Hypertension. GLOMERULONEPHRITIS. In acute *diffuse glomerulonephritis*, hypertension is usually of acute onset, moderate degree, and short duration, it is invariably accompanied by anasarca or edema, a puffy face, hematuria, proteinuria, oliguria, backache, malaise, and low fever, it is preceded by a history of septic sore throat, scarlet fever, or other infection. Blood pressure usually returns to normal within 2 to 7 weeks. The urine is red, dirty-brown, or smoky, and contains albumin, red cells, and blood casts, the blood shows urea retention and multiple evidence of impaired renal function The acute onset of hypertension may cause left ventricular failure, or left and right failure, retinopathy, or encephalopathy.

Chronic diffuse glomerulonephritis, which may follow an acute or subacute phase of nephritis, a nephrotic syndrome, or a "leaky" kidney with albuminuria, is invariably accompanied by hypertension and is associated with renal insufficiency The hypertension of chronic nephritis may be moderate or severe; it is usually fixed and may attain levels of over 250 systolic and 150 diastolic, it is associated with high blood urea, nonprotein nitrogen, and creatinine, anemia, and proteinuria; hyaline, granular, and epithelial casts, and red blood cells are found in the urine. With a tendency to increasing renal and cardiac insufficiency, the disease usually terminates, after a variable course, in fatal uremia.

Sustained or persistent hypertension, otherwise indistinguishable from essential hypertension, occurs more frequently in pheochromocytoma than does the classical, paroxysmal form of hypertension. Adrenal tumors associated with persistent hypertension are usually small and have a total catecholamine content of less than 80 mg, 90 to 97 per cent of which is norepinephrine (Goldenberg, 1950). They are either completely asymptomatic or associated with bizarre symptoms or symptoms suggestive of malignancy or Addison's disease. The hypertension may or may not be associated with symptoms and signs of hypermetabolism and hyperglycemia. One may suspect the adrenomedullary origin of the hypertension if there is history of paroxysmal attacks of hypertension, hyperglycemia with glycosuria, abnormal glucose tolerance curves, tachycardia, postural hypotension, low-grade pyrexia, normal reaction to cold-pressor stimuli, leucocytosis, raised basal metabolic rate, and positive (radiologic, chemical, or pharmacologic) screening tests. In the absence of these features, the condition is likely to be mistaken for essential hypertension.

DIAGNOSIS. Diagnosis of medullary hyperfunction is of the utmost importance, because of its possible surgical correction. It is based on certain typical clinical features and special diagnostic tests:

Radiologic Tests. Roentgenograms of the abdomen may reveal or outline a mass, provided it is not too small or anomalously situated, and especially when it is calcified. At times, secondary spreads of the tumor, if malignant, may be detected by radiography. Tomography or planigraphy, after perirenal insufflation with air or oxygen, may disclose the outlines of the tumor. On rare occasions, an x-ray of the chest may reveal ... [illegible]

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t ... [illegible] ... cent of pheochromocytomas. They depend on the use of (1) adrenergic blocking agents (adrenolytic drugs or antagonists to catecholamines), such as Regitine (pentolamine) and Benzodioxane (Piperoxan), (2) adrenal stimulants or pressor agents, such as histamine acid phosphate base, Mecholyl, hexamethonium bromide, and tetraethylammonium chloride.

Regitine Test. Although less specific, Regitine is usually prefer... [illegible]

less likely [illegible]

rise of bl... [illegible] ... A drop of pressure of over 35/25, after an intravenous injection of 5 mg of the drug, is considered diagnostic. *False-positive reactions* may be noted after sedatives or narcotics, and in patients with malignant, renal, or essential hypertension. *False-negative reactions* may be due to administration of Apresoline or other hypotensive drugs; therefore, such drugs must be discontinued for a week before the test.

Histamine Test. In normotensive and mildly hypertensive subjects with suspected medullary hyperfunction, an intravenous injection of 0.025 to 0.05 mg histamine acid phosphate (or of 300 mg tetraethylammonium chloride or 15 mg hexamethonium bromide) may help to confirm the diagnosis by provoking a hypertensive crisis.

Chemical Tests. A direct, chemical determination of the catecholamine (norepinephrine and epinephrine) content of blood or urine (24-hr excretion) is the most dependable of all tests for pheochromocytoma. The urinary excretion of sympathomimetic amines may rise in such cases from the normal of 14 to 40 mg norepinephrine to between 600 and 2,700 mg/day. A *false-positive reaction* may arise at times from raised intracranial tension, renal insufficiency, or anxiety neurosis.

Exploratory Laparotomy. A laparotomy may prove necessary in suspected cases of pheochromocytoma, not only to establish the diagnosis or locate the tumor, but as a preliminary measure prior to surgical removal.

TREATMENT. The hypertension of pheochromocytoma responds promptly or dramatically to surgical removal of the tumor. It should be kept in mind that the operation, even if carried out with every possible precaution (such as slow intravenous drip of norepinephrine), carries a high mortality rate.

Menopausal Hypertension. The incidence of menopausal hypertension has been variously reported as between 1 and 50 per cent. It is a mild and benign form of hypertension, which may be either transitory or persistent, and is associated with a host of symptoms, such as irregular or scanty periods, hot flushes, feeling of cold, palpitation, emotional instability, and fine tremors, and is common in women during the menopause. When menopausal hypertension occurs in conjunction with obesity, osteoarthritis of the knee joints, and tender subcutaneous nodules, the syndrome is called Gram's syndrome.

P... [illegible]

ing [illegible]

It ... [illegible] ... one of several causes: (1) pregnancy toxemia, either preeclamptic or eclamptic; (2) essential hypertension, associ-

sodium, a persistently alkaline urine with low and fixed specific gravity, normal 17-hydroxycorticoid, 11-oxysteroid, and 17-ketosteroid excretions, and an increased content of aldosterone. The hypertension, even when severe or malignant, usually responds to surgical removal of the tumor.

SECONDARY ALDOSTERONISM. Hypersecretion of aldosterone, of noncortical origin, may arise in states of generalized edema, such as congestive failure, nephrosis, or liver cirrhosis It may occur after excessive loss of fluid, as in neglected diabetes mellitus, diabetes insipidus, or salt-losing nephritis; after excessive administration of diuretics (such as mercurials or Diamox); or after violent exercise, salt-free diet, or venesection

ADRENOGENITAL SYNDROME A rare syndrome of cortical hypersecretion, associated with androgen-estrogen imbalance, may be caused by tumor or hyperplasia of the adrenal cortex, hypothalamic disease, pineal tumor, ovarian disease, or Leydig cell testicular tumor It is characterized by hypertension, *virilism*, *hirsutism*, small breasts, amenorrhea, and enlarged clitoris in women; by feminization, small genitals, and loss of libido in men While urinary excretions of 17-ketosteroid and estrogen are increased, that of 11-17-oxysteroid remains unaltered. Unlike all other forms of hypertension, adrenogenital hypertension may be relieved by the oral administration of cortisone or *prednisone*.

DIAGNOSIS The recognition of adrenal hypercorticism depends on the general appearance of the patient, sexual characteristics, hypertension, weakness, fatigability; steroid (17-ketosteroid, 11-oxysteroid, 17-hydroxycorticoid, and aldosterone) content of blood and urine, biochemical alterations of blood and urine (including carbon dioxide, chloride, sodium, potassium, pH, protein-bound iodine, sugar, and catecholamines); excretory pyelograms, x-rays of adrenal glands, perirenal insufflation with oxygen; and exploratory laparotomy.

Pheochromocytoma (*Adrenomedullary Hypertension*). Numerous cases of pheochromocytoma, associated with paroxysmal or sustained hypertension, have been reported in medical literature since Frankel's description (1886). It is an interesting, but infrequent, usually benign tumor, arising from the chromaffin cells or pheochromocytes of one or both adrenal medullas (in 90 per cent of cases) or from extramedullary sites, such as the pa ganglia (embedded within the sympathe ganglia), and the aortic chromaffin bodies organ of Zuckerkändl, at the root of the in rior mesenteric artery). The pheochromo toma (or *chromaffinoma*), by discharging cessive amounts of normal catecholamines (inephrine and norepinephrine), is the cause an interesting form of hypertension. The tun is usually a circumscribed, spherical or ov solid, tan-colored or grayish-white mass, u ally single (in 90 per cent of cases) a benign (in 90 per cent), arising at any a from 20 to 50 years (with a peak incidence the age of 44 years). It may arise in conju tion with neurofibromatosis or the Stur Weber syndrome.

The *hypertension occurs* in about 0.5 cent of all cases of hypertension, and may either paroxysmal or persistent. Paroxysm attacks of hypertension, when arising in p ochromocytoma, are almost pathognomon Arising either spontaneously (usually in morning hours) or after exercise, emotion, eration, or abdominal palpation, the *paroxys of hypertension*, which usually last for 5 30 min (for days at times), occur cyclically irregularly, from several times a day to on or twice a year. They are characterized by sudden and steep rise of both the systolic a the diastolic blood pressure. They are, as rule, associated with severe and generaliz headache, drenching sweat, tremors, palpi tion, pallor or cyanosis, vasomotor phenome of the skin, paresthesias, dilated pupils, naus vomiting, abdominal cramps, rapid beating the heart, extrasystoles, postural hypotensi restlessness, nervousness, low-grade pyrex albuminuria, increase of basal metabolic r (about +20 or more), glycosuria, and h perglycemia The clinical manifestations a caused by the excessive liberation in the blo of norepinephrine [which tends to cause d fuse vasoconstriction, bradycardia, and systo and diastolic hypertension (without changes cardiac output)] and epinephrine [which ten to cause diffuse vasodilatation (except in t vessels of skin, kidneys, and lungs), systo hypertension, diastolic hypotension, tachyca dia, and increased cardiac output]. The hype tensive paroxysms of pheochromocytoma us ally subside spontaneously, being followed times by facial flushing and generalized wea ness.

ated with or aggravated by the state of pregnancy; (3) urologic complication of pregnancy, such as pyelonephritis or glomerulonephritis; (4) sodium and water retention.

HYPERTENSION OF PREGNANCY TOXEMIA. It frequently occurs during the third trimester of pregnancy (earlier, at times, in association with vesicular mole) or just after delivery and is particularly common in women with renal disease The increase of pressure is usually moderate and is associated with sudden gain in body weight and severe edema (particularly of the face and hands). There are massive albuminuria, abundant red cells and casts in the urine, early retinopathy with vascular spasm, convulsions or (when associated with eclampsia) positive Ascheim-Zondek test, increase of blood uric acid, low serum albumin, and normal blood urea (unless the form is complicated by kidney disease, malignant hypertension, or adrenal necrosis). Although associated with a mortality rate of over 25 per cent for the fetus and of 1 to 2 per cent for the mother, pregnancy toxemia promptly responds to artificial termination of the pregnancy.

The etiology of hypertension in pregnancy toxemia remains obscure in spite of numerous investigations The two most favored viewpoints attribute the hypertension to (1) placental ischemia or premature vascular aging of the placenta, causing absorption of autolytic pressor substances, or (2) hormonal imbalance, caused by a primary metabolic or vascular anomaly of the placenta, and leading to early senility, with premature withdrawal of steroid hormones

NEUROGENIC HYPERTENSION

Lesions of the central or autonomic nervous system, when involving the vasomotor centers of the diencephalon, pons, or medulla, or when associated with raised intracranial tension, may bring about arterial hypertension, somewhat similar to that of pheochromocytoma

Neurogenic or cerebral hypertension, as in adrenomedullary hyperfunction, is either paroxysmal or sustained and is likely to develop into hypertensive encephalopathy or the malignant syndrome. It is frequently associated with symptoms and signs of sympathetic hyperactivity, such as flushing, sweating, tachycardia, abdominal pain, and vasomotor phenomena Because of the frequently increased catecholamine content of the blood and the prompt response to sympatholytic drugs, hypertension of neurogenic origin is said to be mediated through the sympathetic system.

Hypertensive Diencephalic Syndrome (Page). This is a syndrome of young or middle-aged women with labile hypertension and symptoms similar to those induced by stimulation of the diencephalon in man. The syndrome is associated with hypertensive episodes, patchy blushing of the face and upper part of the chest, cold and dusky, blue or pale extremities, localized sweating, lacrimation, tachycardia, increased basal metabolic rate, and hyperperistalsis The attacks may arise spontaneously or after emotional excitement, and may lead to an erroneous diagnosis of thyrotoxicosis. Subtotal thyroidectomy fails to improve the condition.

The differential diagnosis between neurogenic and adrenomedullary hypertension may prove extremely difficult because of the common feature of paroxysmal hypertension The diagnosis of neurogenic hypertension may have to depend on the demonstration of the primary neurologic disease, exclusion of adrenomedullary overaction, x-ray of skull and abdomen, electroencephalographic and cerebrospinal fluid examinations, arteriograms, ventriculograms, and demonstration of lead or porphyria in the urine

Treatment Neurogenic hypertension may be treated by removal of the causative lesion (when possible), administration of sympatholytic drugs, or tapping of cerebrospinal fluid, in order to reduce the intracranial tension.

COARCTATION OF AORTA

This condition is discussed in Part 6, Chaps 2 and 3

tricular strain A *heaving apex beat* and an *increased long diameter of the heart* reveal hypertrophy of the left ventricle A *triple rhythm* (*gallop rhythm*) is evidence of left ventricular strain and of increased left atrial pressure It may be of either the ventricular or the atrial type owing to respective intensification of either the 3d or the 4th heart sound. The meaning of both types is similar, because in the first case, the triple rhythm indicates stronger atrial contraction, in the second, more tumultuous passive ventricular filling In both cases, there is a higher left atrial pressure.

Systolic apical and aortic murmurs are common. The first reveals some dilatation of the mitral ring; the second, some dilatation of the aorta. If mitral valvular sclerosis is excluded (recent appearance of the murmur), the apical murmur is evidence of left ventricular strain and, possibly, of failure. As far as the aortic murmur is concerned, it simply indicates a high level of arterial pressure and a "relative" aortic stenosis (flow murmur).

A ringing 2d aortic sound is the direct result of hypertension It may be followed by a *short, blowing, diastolic murmur*, probably due to some degree of sclerosis of the aortic leaflets

Even though the borderline between left ventricular hypertrophy, left ventricular strain, and left ventricular failure is not always easy to draw, especially on purely clinical grounds, certain symptoms and signs indicate more severe repercussions on the heart, and definite failure (Table 12-3).

Orthopnea and *paroxysmal dyspnea* involve a complex cardiovascular and reflex mechanism which is partly based on the results of increased residual blood within the left ventricle, increased left atrial and pulmonary venous pressures, and higher right ventricular and pulmonary arterial pressures In other words, the various elements of the paroxysm lead to a readjustment of work whereby the right ventricle increases its work and maintains a high pressure, the pulmonary circulation is distended, and the left atrial filling pressure is greater. The left ventricle dilates, and the greater length of its fibers allows an increase of work A *loud* P_2 is usually heard if this readjustment of pressures becomes permanent.

Paroxysmal pulmonary edema of the hypertensive patient has a complex mechanism. Its underlying phenomena are left ventricular strain and consistently high pulmonary arterial and venous pressures (see Part 18, Chap. 13). Usually, one of several mechanisms leads to peripheral vasoconstriction, redistribution of the blood, and sudden congestion of the lungs. However, several other complex phenomena, including reflex and humoral elements, are involved in the production of the attack.

Among the signs of left ventricular failure, *tachycardia* is common. *Pulsus alternans* has a severe meaning, *revealing a profound* biochemical deterioration of the myocardium. *Pulmonary rales* indicate subacute *pulmonary* edema. A *diastolic rumble at the apex and* midprecordium is probably due to severe dilatation of the left *ventricle with "relative"* mitral stenosis It may be a transitory murmur and disappear after a few weeks with improvement of the cardiac condition It is more common in cases with coronary heart disease and diffuse fibrosis of the left ventricle.

THE ELECTROCARDIOGRAM

The electrocardiogram is useful in ascertaining whether or not there are cardiac repercussions of hypertension. It may reveal *evidence of left ventricular hypertrophy* consisting of *increased voltage of the QRS complex in the limb leads* (with deeper S wave in V_1 to V_2 and taller R wave in V_5 to V_6); *increased duration of the QRS* complex, which reaches 0 10 to 0 11 sec in the limb leads; *and a delay of the R* wave over the Q wave in V_5 to V_6 greater than 0.05 sec.

Other laboratory data may be of importance (see the classification on page 12–46).

THE PHONOCARDIOGRAM

The phonocardiogram may reveal the existence of an *apical systolic murmur* (relative mitral insufficiency), an *apical diastolic murmur* (*relative* mitral stenosis), or both (Fig. 12-3). The latter can be differentiated from the murmur of organic mitral stenosis through positive data (high voltage, late appearance, wide diffusion, initiation by the vibration of a large 3d sound) and negative data (lack of an opening snap of the mitral valve, normal interval between the Q wave and 1st sound). It may also reveal *an aortic systolic murmur* and an aortic *diastolic murmur.* The former is seldom diamond-shaped, it is usually short and

7

Graphic data in hypertension

ALDO A. LUISADA

Arterial hypertension may or may not be accompanied by obvious changes of cardiac function. While it is logical to admit that sustained hypertension always leads to some degree of left ventricular hypertrophy, the latter may be so mild that no evidence can be found during life and only autopsy may reveal a slight increase in the weight of the heart, in the thickness of the left ventricular wall, and in the length of the outflow chamber of the left ventricle.

Although symptoms and signs have already been described, a brief listing of them will be useful here (Table 12-3) because graphic data necessarily reflect changes also revealed by clinical data.

The repercussions of hypertension may include exertional dyspnea, palpitation or precordial pain, dry cough, and sleeplessness

Dry cough may be caused by a reflex from the aortic arch or carotid sinus receptors *Sleeplessness* may be a purely cerebral disturbance. Therefore, neither of these symptoms, per se, indicates cardiac involvement *Exertional dyspnea* and *palpitation* are usually evidence of some decrease of cardiac reserve and, therefore, are the result of the constant high load placed upon the left ventricle. *Precordial pain* reveals the increased blood demand of the left ventricle, which is further increased by exertion. As it indicates coronary insufficiency, e.g , a disproportion between blood supply and blood demand, it is more likely to occur when there is some degree of coronary rigidity due to atherosclerosis.

The physical signs of *cardiac repercussions* include the following.

Premature ventricular contractions, a second cause of palpitation, are revealed by irregularities of the pulse and of the heart sounds. They indicate increased excitability of the myocardium, usually occurring in the stage of ven-

TABLE 12-3 CARDIAC SYMPTOMS AND SIGNS OF HYPERTENSIVE HEART DISEASE AND LEFT VENTRICULAR FAILURE

Hypertensive Heart Disease		*Left Ventricular Failure*	
Symptoms	*Signs*	*Symptoms*	*Signs*
Exertional dyspnea Palpitation Dry cough Sleeplessness Precordial pain	Premature contractions Heaving apex beat Triple rhythm (gallop) Systolic apical and aortic murmurs Ringing A_2 followed by a short blowing murmur	Orthopnea Paroxysmal dyspnea (Paroxysmal pulmonary edema)	Tachycardia Loud P_2 Pulsus alternans Diastolic apical rumble Basal pulmonary rales

tricular strain A *heaving apex beat* and an *increased long diameter of the heart* reveal hypertrophy of the left ventricle A *triple rhythm (gallop rhythm)* is evidence of left ventricular strain and of increased left atrial pressure. It may be of either the ventricular or the atrial type owing to respective intensification of either the 3d or the 4th heart sound. The meaning of both types is similar, because in the first case, the triple rhythm indicates stronger atrial contraction, in the second, more tumultuous passive ventricular filling. In both cases, there is a higher left atrial pressure

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Paroxysmal pulmonary edema of the hypertensive patient has a complex mechanism Its underlying phenomena are left ventricular strain and consistently high pulmonary arterial and venous pressures (see Part 18, Chap. 13). Usually, one of several mechanisms leads to peripheral vasoconstriction, redistribution of the blood, and sudden congestion of the lungs However, several other complex phenomena, including reflex and humoral elements, are involved in the production of the attack.

Among the signs of left ventricular failure, *tachycardia* is common. *Pulsus alternans* has a severe meaning, revealing a profound biochemical deterioration of the myocardium. *Pulmonary rales* indicate subacute pulmonary edema. A *diastolic rumble* at the apex and midprecordium is probably due to severe dilatation of the left ventricle with "relative" mitral stenosis It may be a *transitory murmur* and disappear after a few weeks with improvement of the cardiac condition It is more common in cases with *coronary* heart disease and diffuse fibrosis of the left ventricle.

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Other laboratory data may be of importance (see the classification on page 12–46).

THE PHONOCARDIOGRAM

The phonocardiogram may reveal the existence of an *apical systolic murmur* (relative mitral insufficiency), an *apical diastolic murmur* (relative mitral stenosis), or both (Fig 12-3) *The* latter can be differentiated from the murmur of organic mitral stenosis through positive data (high voltage, late appearance, wide diffusion, initiation by the vibration of a large *3d sound*) and negative data (lack of an opening snap of the mitral valve, normal interval between the Q wave and 1st sound). It may also reveal an *aortic systolic murmur* and an *aortic diastolic murmur.* The former is seldom diamond-shaped, it is usually short and

7

Graphic data in hypertension

ALDO A. LUISADA

Arterial hypertension may or may not be accompanied by obvious changes of cardiac function. While it is logical to admit that sustained hypertension always leads to some degree of left ventricular hypertrophy, the latter may be so mild that no evidence can be found during life and only autopsy may reveal a slight increase in the weight of the heart, in the thickness of the left ventricular wall, and in the length of the outflow chamber of the left ventricle.

Although symptoms and signs have already been described, a brief listing of them will be useful here (Table 12-3) because graphic data necessarily reflect changes also revealed by clinical data.

The repercussions of hypertension may include exertional dyspnea, palpitation or precordial pain, dry cough, and sleeplessness

Dry cough may be caused by a reflex from the aortic arch or carotid sinus receptors *Sleeplessness* may be a purely cerebral disturbance. Therefore, neither of these symptoms, per se, indicates cardiac involvement *Exertional dyspnea* and *palpitation* are usually evidence of some decrease of cardiac reserve and, therefore, are the result of the constant high load placed upon the left ventricle. *Precordial pain* reveals the increased blood demand of the left ventricle, which is further increased by exertion. As it indicates coronary insufficiency, e.g., a disproportion between blood supply and blood demand, it is more likely to occur when there is some degree of coronary rigidity due to atherosclerosis.

The physical signs of *cardiac repercussions* include the following.

Premature ventricular contractions, a second cause of palpitation, are revealed by irregularities of the pulse and of the heart sounds. They indicate increased excitability of the myocardium, usually occurring in the stage of ven-

TABLE 12-3 CARDIAC SYMPTOMS AND SIGNS OF HYPERTENSIVE HEART DISEASE AND LEFT VENTRICULAR FAILURE

Hypertensive Heart Disease		*Left Ventricular Failure*	
Symptoms	*Signs*	*Symptoms*	*Signs*
Exertional dyspnea Palpitation Dry cough Sleeplessness Precordial pain	Premature contractions Heaving apex beat Triple rhythm (gallop) Systolic apical and aortic murmurs Ringing A_2 followed by a short blowing murmur	Orthopnea Paroxysmal dyspnea (Paroxysmal pulmonary edema)	Tachycardia Loud P_2 Pulsus alternans Diastolic apical rumble Basal pulmonary rales

PULSE TRACINGS

Pulse tracings may reveal the existence of *pulsus alternans*, a phenomenon having a serious meaning, even though patients with this typical abnormality may improve and even recover. They may show the results of irregularities of the cardiac rhythm, usually caused by ventricular premature contractions.

BALLISTOCARDIOGRAM

The *ballistocardiogram* (BCG) usually has large complexes in hypertension without severe strain Whenever the heart is undergoing strain or failure, several abnormalities can be noticed It is difficult to separate the parts played by atherosclerosis of the aorta, abnormal left ventricular contraction, and peripheral vasoconstriction in causing the abnormal patterns which can be observed Undoubtedly, the more atypical the pattern, the less favorable the prognosis

CIRCULATION TIMES—RADIOCARDIOGRAPHY

Circulation times are normal as long as the left ventricle is not failing When the left ventricle fails, *arm-to-tongue time* (Decholin) becomes longer while *arm-to-lung time* (ether) is still normal The prolongation of the former is largely due to increase of the residual blood left in the left ventricle at the end of systole and to slower circulation from the pulmonary capillaries, through the left heart, to the arteries of the systemic circulation. A similar mechanism causes a prolongation of the L wave of the *radiocardiogram* (Fig. 12-5), which is a witness to the longer persistence of injected radioactive materials within the left ventricle. The valley between the R and L waves becomes less marked.

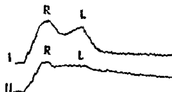


Fig. 12-5. Scheme of the radiocardiogram in hypertensive heart disease. I, normal; II, left ventricular failure; prolongation of L wave; less evident drop of curve between R and L waves.

The following schema presents all the above data in their progressive sequence and in order of increased severity.

PROGRESSIVE EVIDENCE OF CARDIAC EFFECTS OF HYPERTENSION

1. Exertional dyspnea, palpitation, cough, premature beats, heaving apex beat, ECG evidence of hypertrophy, systolic basal murmur, ringing A_2, large BCG waves
2. Tachycardia, systolic apical murmur, triple rhythm, ECG evidence of anterolateral ischemia, x-ray signs of enlarged left ventricle
3. Paroxysmal dyspnea, prolonged 1st apical sound, diastolic apical rumble, short aortic diastolic murmur, atypical BCG pattern, ECG evidence of bundle branch block or intraventricular block, increased arm-to-tongue time, pulsus alternans
4. Orthopnea, paroxysms of pulmonary edema, x-ray evidence of total cardiac enlargement, increased circulation times, small BCG waves, evidence of venous and hepatic engorgement

LABORATORY DATA REVEALING HYPERTENSIVE HEART DISEASE

1. ECG
   a. Evidence of left ventricular hypertrophy
   b. Evidence of anterolateral ischemia
   c. Evidence of diffuse coronary insufficiency
   d. Evidence of myocardial fibrosis

2. Phonocardiogram
   a. Apical murmurs: Systolic Diastolic
   b. Aortic murmurs: Systolic Diastolic
   c. Triple rhythm
   d. Prolonged 1st sound
   e. Loud (split) 2d aortic sound

3. X-ray
   a. Convexity of left ventricular border
   b. Elongation of cardiac shadow (posterior enlargement)
   c. Increased pulsations of aorta (small pulsations of left ventricle)

4. Low-frequency tracing
   a. Positive, tall apical pulsation
   b. Negative epigastric pulsation

5. BCG
   a. Large waves, small waves
   b. Abnormal pattern

6. Circulation time or radiocardiography
   a. Prolonged arm-to-tongue
   b. Delayed end of L wave

consists of two to three extremely low-pitched vibrations (aortic vibrations) with superimposition of other, higher-pitched vibrations in early systole. The latter is also usually short (three to six vibrations in decrescendo) and starts with a 2d sound of increased magnitude (Fig. 12-3).

While the basal murmurs are the direct result of hypertension and have no special meaning, the apical murmurs result from dilatation of the left ventricle and indicate progressive deterioration from strain to failure. The diastolic murmur carries with it a more serious meaning than the systolic. In its interpretation, it should be kept in mind that severe coronary heart disease or syphilitic aortic insufficiency may favor it.

A *triple rhythm (gallop rhythm)* is a common finding. It may be caused by intensification or higher pitch of either the 3d or the 4th sound. Larger magnitude, higher pitch, and more numerous vibrations indicate more serious functional strain and a higher left atrial pressure—therefore, a proportionally more serious prognosis.

THE LOW-FREQUENCY TRACINGS OF THE PRECORDIUM AND EPIGASTRIUM

These tracings may supply data indicating enlargement of the left ventricle. When this chamber is enlarged through hypertrophy and dilatation, the tracing recorded at the apex (old term, *apex cardiogram*) reveals a tall, squarish or conical plateau in systole, frequently preceded by a high presystolic wave (atrial contraction). On the other hand, the *epigastric tracing* presents a deep, inverted wave in systole, which at times is like a mirror image of that of the apex (Fig. 12-4). These findings are due to the powerful contraction of the heart (the apex moves forwards and upwards during systole) and also to the stronger atrial contractions.

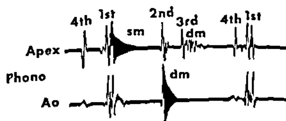


Fig. 12-3. Scheme of possible changes of phonocardiogram in hypertension. Apex, large 4th (atrial) sound causing a triple rhythm; faint systolic murmur, large 3d sound with "functional" diastolic rumble. Aorta, large 2d sound, short, early diastolic murmur.

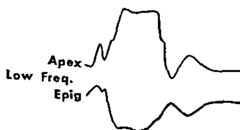


Fig. 12-4. Scheme of the low-frequency tracings in hypertension. Positive plateau at apex, negative pulsation at epigastrium, indicating left ventricular enlargement.

jor culprit and that lowering of blood pressure can delay or reverse many of the pathologic sequelae of hypertension.

SELECTION OF PATIENTS REQUIRING HYPOTENSIVE THERAPY

In general, if the disorder has been present for 8 years or more, and in that time no evidence of cerebral disease has become apparent, the arterioles of the optic fundi show only mild arteriolar changes without hemorrhage, exudate, or papilledema, the heart is within normal size, the electrocardiogram is normal or shows only left axis deviation, and the urine is free of albumin, it is clear that the disease is following a benign course and there is no indication for drastic therapy. Reassurance, simple sedation (e g , barbiturates), and reasonable rules of healthy, temperate living are adequate treatment Patients of this type will, on the average, live to within 3 to 4 years of their normal life expectancy without any treatment

On the other hand, individuals with hypertension of less than 8 years' duration who already show cardiac involvement (such as marked cardiac hypertrophy, left ventricular hypertrophy on the electrocardiogram, precordial pain, congestive failure), or severe changes in the optic fundi (hemorrhage, exudate, or papilledema), or evidence of cerebrovascular disease, or albuminuria have shown that they cannot tolerate their current levels of blood pressure. They probably have some degree of associated atherosclerosis as well. These patients with clear evidence of hypertensive cardiovascular disease should receive treatment.

There is no disagreement that patients in the accelerated or malignant phase of hypertension should be treated, there is little disagreement that patients with overt evidence of cerebral, cardiac, or renal involvement from hypertension should be treated Patients in this latter group who have required from 15 to 25 years to develop these complications can be assumed to have a considerable degree of atherosclerosis. Decision concerning therapy is most debated in the young or middle-aged person with labile blood pressure or with fixed high diastolic levels At present, patients with labile blood pressure should be treated with the safest of the sedative or "tranquilizing" drugs, fixed high diastolic pressure, especially in the young or middle-aged male, requires therapy. Too often these patients, "benign" by the usual criteria of lack of objective evidence of hypertensive cardiovascular disease, develop cerebral attacks, myocardial infarction, or renal insufficiency. There is not as yet any proof that hypotensive therapy will avert these untoward events but, in the absence of specific therapy, it seems worthwhile to attempt to lower the blood pressure.

AIM OF THERAPY

Some patients with hypertension have demonstrated their tolerance of the disease and should not be treated with potent hypotensive agents. Elderly persons, especially those with a history of long-standing hypertension (15 years or more) and *no evidence of hypertensive disease* other than moderate enlargement of the left ventricle, or mild arteriolar *changes in the* optic fundi, should be left free of dietary or drug restrictions. Patients with systolic elevations but diastolic levels of *100 or less*, especially if they are 60 years of age or older, require no hypotensive medication. Persons in their twenties without symptoms and with no signs but mild elevations of blood pressure usually require only supportive psychotherapy to prevent a hypertension neurosis

CHOICE OF THERAPY

The multiplicity of therapies indicates that none is ideal and that there is no general agreement on their use However, *each has* some value, and when they are properly used, often in combination, they can modify favorably many of the unfortunate *sequelae* of hypertension. Current therapy includes (1) psychotherapy, (2) diet, (3) drugs, (4) surgery.

PSYCHOTHERAPY[1]

Much of the effect on symptoms and blood pressure level formerly attributed to drugs, diet, and surgery is due to *the psychodynamics* of the doctor-patient relationship. When this relationship is wisely used by the physi-

[1] The psychologic aspects of hypertension have been discussed in Chap 2. *Editor.*

Treatment of the hypertensive states

EDWARD MEILMAN

The remarkable variety of potent hypotensive drugs and measures now available has placed new responsibilities on the physician caring for patients with hypertensive cardiovascular disease. Less than a generation ago, the medical armamentarium consisted of sedatives (such as barbiturates and bromides), vasodilators (such as nitrites and xanthines), thiocyanates, and reassurance The real advantages and the technique of stringent salt restriction proposed by Allen (1920) did not have wide recognition In fact, diet was recommended only for obesity Removal of portions of the sympathetic nervous system had begun The still unsolved problem of suitable case selection appeared early in the history of this operation. The action of placebos and other psychotherapeutic measures on blood pressure levels had been clearly delineated, with proper emphasis placed on the relation of home and office blood pressure readings The personality disorders in many patients with hypertension were appreciated, but the concept that emotional stresses could convert hypertension into an accelerated phase was new

At present, a growing list of drugs, various forms of low-salt diet, psychotherapy, and surgery of the adrenal glands and of the sympathetic nervous system require consideration of their proper role in the therapy of hypertensive cardiovascular disease. Except for rare instances of specific kinds of hypertension amenable to surgical cure (coarctation, adrenal tumors, unilateral renal disease), the selection of the proper modality of treatment remains entirely empirical and largely a matter of trial and error. These measures are not simple to select and administer, nor are they successful in every case

Despite marked differences in their mechanism of action, all the measures thus far suggested as therapy in hypertension share in varying degree the ability to lower arterial blood pressure Thus the advisability and results of lowering blood pressure must be examined before the specific therapies themselves

THE EFFECT OF LOWERING BLOOD PRESSURE

For many years, and to some extent today, objections have been raised to hypotensive programs because of evidence that atherosclerosis can progress and kill despite lowered blood pressure, and belief that the process is neither ameliorated nor delayed by lowering the blood pressure Moreover, it has been claimed that lowering blood pressure may deprive the tissues beyond constricted or organically narrowed arterioles of adequate nourishment For example, coronary disease may progress following a sympathectomy; falls in blood pressure, especially when sudden and severe, and accompanied by shunting of large volumes of blood into venous areas, may precipitate precordial pain and even myocardial infarction, as well as cerebral thrombosis and infarction There is, however, a growing body of clinical and laboratory evidence indicating that the elevated blood pressure itself is a ma-

its effectiveness in restoring vision will give some patients the motivation to remain on it for long periods For most patients, the greatest usefulness of the rice diet is to promote acceptance of a 200-mg-sodium diet. It is now well recognized that the effectiveness of the rice diet depends on its low sodium content. As long as the daily sodium intake is 500 mg or less, about one-fourth of the patients may be expected to have a favorable response. Raising the daily intake above 500 mg usually results in a rise of blood pressure Measurement of 24-hr excretion of sodium is important in differentiating blood pressure fall from diet versus blood pressure fall in response to the psychic effects of a somewhat bizarre program At present, there seems to be no clear advantage of the rice diet over a 200-mg-sodium diet. In either case, and especially in the presence of renal disease, determination of the electrolytes in the blood should be carried out at intervals to observe whether low serum sodium and nitrogen retention are occurring Mercurials, carbonic anhydrase inhibitors (Diamox), ammonium chloride, and cation-exchange resins have been recommended as adjuncts to sodium restriction Although these measures may mitigate some of the harshness of a 200-mg-sodium diet, they do not allow the patient to eat normally. Resins introduce other problems, since they cannot remove sodium selectively. Losses of potassium, calcium, and magnesium occur, together with metabolic acidosis

For patients with heart failure, malignant hypertension, or even uncomplicated hypertension, sodium restriction alone is often effective This program is worth following only in patients with severe degrees of hypertension or with evidence of vascular disease, such as grade III or IV eye grounds, enlarged heart with congestive failure or coronary artery disease, or early renal disease. The only contraindication is a significant degree of renal failure

DRUGS

The need for a suitable oral preparation for the control of elevated blood pressure has led to a revival of interest in old drugs as well as search for new, synthetic ones. Some drugs stimulate the afferent side of reflex vasodepressor mechanisms (the *veratrum* esters); some inhibit sympathetic activity centrally (dihydrogenated *ergot* alkaloids); some act centrally and also peripherally, probably against circulating pressor agents (*hydrazinophthalazine*); some act on efferent pathways by paralyzing cholinergic transmission at autonomic ganglia (*ganglionic blocking* agents) or act directly on the smooth muscle of the arterioles to prevent the usual response to circulating sympathetic pressors (*dibenamine* compounds); some have not only a central, hypothalamic action but a complex effect on other tissues (*rauwolfia* derivatives).

Rauwolfia serpentina. The newest and most intriguing of the hypotensive drugs comes from *Rauwolfia serpentina*. This drug has been used in India primarily for its psychiatric sedative effects on disturbed persons. In 1942 its moderate hypotensive properties were described by Indian workers, and in 1953 Wilkins introduced this drug into the United States. Since then, it has had extensive trial in hypertension and in many psychiatric conditions. The crude root, standardized alkaloidal extracts, and the pure alkaloids (*reserpine, rescinnamine, deserpidine*) seem to have similar pharmacologic properties It has been suggested that the pure alkaloids vary in their production of disagreeable side effects, notably depression. An almost flat dose-response (blood pressure) curve, unique among present hypotensive drugs, indicates that rauwolfia has a remarkable degree of safety. Adults and even children who have ingested large amounts of the drug have suffered only from excessive sedation, diarrhea, and moderate hypotension.

Rauwolfia acts on the central nervous system, presumably at the hypothalamus, and its ability to decrease heart rate and blood pressure suggests either an inhibition of sympathetic or an enhancement of parasympathetic activity. However, orthostatic hypotension occurs only rarely with rauwolfia Pupillary constriction and relaxation of the nictitating membrane are characteristic in animals, in man, nasal stuffiness is common, often resulting in symptoms of a chronic cold, bloody nasal discharge, and even sinusitis and otitis. Additional evidence of parasympathomimetic activity is the increased secretion of hydrochloric acid in the stomach, with obvious implications for patients with peptic ulcer. Increased intestinal motility may result in diarrhea. In ani-

mals, rauwolfia interferes with the reflex blood pressure rise, mediated by the central nervous system, that is the normal response to hypoxia or carotid sinus occlusion. A characteristic effect of these drugs is a decrease in motor activity (animals) and an unusual placidity (man). The sedation induced by rauwolfia has been aptly labeled *tranquillity*, but this passes readily from calmness and languor to severe depression. *Depression* is common with excessive doses, but it has occurred even with doses in the usual clinical range. In mild form, it appears as a lack of initiative or creativeness. In fact the occurrence of depression has been the most serious side effect of these drugs; they are obviously contraindicated if depression already exists Depression is said to be less common with *deserpidine*. The drug-induced depression usually responds after some weeks to withdrawal of the drug, if electric shock therapy is contemplated, at least one week and preferably more should elapse after discontinuing the drug because it lowers the convulsive threshold. Violent nightmares may occur; in the author's experience, some patients have fewer of these on *rescinnamine* than on *reserpine* Partial or total loss of libido in the male is a common problem A few cases resembling paralysis agitans have been noted in association with rauwolfia, as well as with other tranquilizers such as chlorpromazine. Weight gain is common, and in some cases of heart failure has been said to be associated with worsening of the edema

At the molecular level, reserpine appears to be able to displace serotonin, norepinephrine, and probably epinephrine from intracellular binding sites in the brain tissues, the gastrointestinal tract, the platelets, and even the heart. Administration of reserpine to animals causes an increased urinary excretion of 5-hydroxyindoleacetic acid, a metabolite of serotonin. This has naturally suggested that the pharmacologic properties of the drug are due to the release of serotonin. However the demonstration that norepinephrine is also released suggests that the loss of these constrictor agents from the body [illegible] he vascular system from their effec[illegible]

Emphasis on the side [illegible] lfia should not detract fr[illegible] remarkable therapeutic [illegible] and moderate hyp[illegible] claimed to be [illegible]

tensive patients with labile blood pressure, anxiety, tachycardia, and no evidence of vascular disease. Yet, there is often a satisfying response of blood pressure and symptoms of headache, dizziness, insomnia, and nervousness in older persons with "fixed" hypertension associated with evidence of vascular disease.

DOSAGE Orally, the pure alkaloids are given in daily doses of 0.25 to 1.0 mg for 7 to 10 days, after which the daily dose is reduced to 0.1 to 0 25 mg, depending on the response. Parenteral administration (1 to 2 5 mg intravenously or intramuscularly) has the same general effects as the oral, causing sedation and a moderate blood pressure fall lasting about 6 hr. Curiously, in some individuals it may take several weeks for the full hypotensive effect to appear, when the drug is discontinued, its effects may last 1 to 4 weeks, even though the administered drug appears to be excreted in several hours Undesirable side effects are often controlled by omitting the drug for 1 week out of 4 The hypotensive effect can be successfully overcome by ephedrine or phenylephrine Synergistic effects with other hypotensive drugs are difficult to prove, but the bradycardia of rauwolfia tends to overcome the tachycardia of hydralazine, its bowel-stimulating action may mitigate the constipation from ganglionic blocking drugs, and its tranquilizing effects may make veratrum effective with less vomiting Thus, smaller doses of the other drugs can usually be used if rauwolfia is also employed Rauwolfia and its pure alkaloids therefore seem to be worthwhile in early, mild cases if nervousness and tachycardia are prominent, and simple barbiturate sedation or psychotherapy ineffective. In more severe cases with headache, dizziness, or other evidence of hypertensive cardiovascular disease, it may be useful alone but more likely in combination with other drugs The most serious side effect is depression

The Veratrum Alkaloids [Veriloid, Unitenson, Protoveratrine (Veralba)] Medicinal properties have been known for centuries to reside in the *Veratrum* plants Recently, attention has been directed anew to hypotensive properties of pure ester alkaloids as well as crude extracts of the roots. The side effects, as well as the hypotensive action of crude root, biologically standardized extract, or purified esters such as *protoveratrine A and B*, are [illegible]ar However, the narrow [illegible]nge between

therapeutic and toxic doses, characteristic of these drugs, *favors* the use of crystalline substances. The pharmacologic action of these agents has shown the existence of a reflex decrease in heart rate and blood pressure due to afferent stimulation of chemoreceptors in the heart and great vessels (*the Bezold-Jarisch reflex*). The veratrum esters cause a veratrinic response (repetitive electric discharges from a single stimulus) in the chemoreceptors of the carotid sinus, aortic arch, and coronary vessels of the left ventricle. This increase in afferent electrical activity travels over the vagus and carotid sinus nerves to the vasomotor center in the brain, which then causes a diminution in efferent electrical discharges over the splanchnic and presumably other sympathetic nerves, resulting in a generalized vasodilatation and a fall in blood pressure. This vasodilatation is accompanied by a decrease in cerebrovascular and renal resistance. The veratrum alkaloids also block the carotid sinus pressor reflex and may have some direct central nervous system hypotensive action. In cats, it has been shown that *stimulation of the nodose* ganglion is the source of the vomiting reflex. The hypotension is usually accompanied by bradycardia due to a simultaneous reflex increase in vagal activity.

Toxic doses in man cause epigastric and substernal oppression, nausea, vomiting, sweating, severe hypotension, bradycardia, and even *heart block*. The disturbances of heart rate *and* rhythm are vagal phenomena and are blocked by *atropine* (0.5 to 1.0 mg subcutaneously or intravenously) without, as a rule, eliminating the hypotension. Severe hypotension *is* readily overcome by *ephedrine sulfate* (25 to 35 mg subcutaneously) or *other vasoconstrictor drugs*. *Cardiac irregularities are* more likely *in* patients receiving *digitalis* or *quinidine*. At the peak hypotensive effect, there may be transient electrocardiographic changes *such as* T-wave inversion in leads V_3 to V_4. These are reversed by *atropine* but *not by oxygen*, indicating that they also are *reflex* vagal phenomena. The importance *of distinguishing* a toxic *reaction to* veratrum from a myocardial infarction *is apparent*. Severe vomiting *can* be moderated or overcome by *barbiturates* or chlorpromazine. Since there is no *paralysis* of autonomic activity, interference with *postural* reflexes and the cold-*pressor* response *does* not occur. However, *if* severe hypotension has ensued, standing may cause a further fall in blood pressure. *Oliguria* and diminished glomerular filtration rate may occur during hypotension from veratrum drugs, resembling those seen after any sudden fall in systemic pressure, but they are transitory even if the hypotension is maintained. Fluid retention does not occur. *In fact, negative fluid* and sodium balance can be seen in women with toxemia of pregnancy while under continuous treatment with *veratrum*. *The renal* vasodilatation which occurs with veratrum is not associated with increased cardiac output. In some patients with nitrogen retention, cautious lowering of the blood pressure may be achieved with little or no aggravation of the *renal status. In others*, *especially* when uremia is present, veratrum, like other hypotensive agents, will aggravate the renal *insufficiency*. Nonetheless, even in this *group*, *control* of *encephalopathy*, headache, diminishing vision, and heart failure *may be obtained*.

Administered parenterally, the veratrum alkaloids are probably the drugs of choice when prompt *predictable fall in* blood pressure without *rise in* cardiac output or *disturbance of homeostatic* reflexes is desired. *They are virtually* specific for acute hypertensive encephalopathies, the hypertension *and convulsions* of toxemia of pregnancy, *pulmonary* edema occurring in acute glomerulonephritis, and *steroid*-induced hypertension. These *drugs may* be useful in the treatment of *hypertensive pulmonary edema* if conventional *methods fail*. They are *very useful in malignant* hypertension, especially when loss of *vision is* threatened. Of 9 patients with *malignant* hypertension treated with *parenteral protoveratrine*, 5 *had remissions* and were alive 3 to 5 *years later*. Patients with congestive *heart failure* or coronary disease associated *with hypertension* who show a satisfactory *response to* veratrum, alone or combined with *reserpine*, may expect alleviation *of* failure and decrease in angina.

The intravenous dosage of protoveratrine *A and B* is 1.5 to 1.9 µg/kg, with subsequent *doses* of 20 µg at 10-min intervals until a *satisfactory* hypotensive effect is obtained. The hypotension can be maintained for hours by continuous intravenous *infusion* at the rate of about 1 µg/min. The *duration of action* of a single effective *intravenous injection* (average dose 100 µg) is 1 *to* 3 *hr*. Subcutaneous or

mals, rauwolfia interferes with the reflex blood pressure rise, mediated by the central nervous system, that is the normal response to hypoxia or carotid sinus occlusion. A characteristic effect of these drugs is a decrease in motor activity (animals) and an unusual placidity (man). The sedation induced by rauwolfia has been aptly labeled *tranquillity*, but this passes readily from calmness and languor to severe depression. *Depression* is common with excessive doses, but it has occurred even with doses in the usual clinical range In mild form, it appears as a lack of initiative or creativeness. In fact the occurrence of depression has been the most serious side effect of these drugs, they are obviously contraindicated if depression already exists. Depression is said to be less common with *deserpidine* The drug-induced depression usually responds after some weeks to withdrawal of the drug, if electric shock therapy is contemplated, at least one week and preferably more should elapse after discontinuing the drug because it lowers the convulsive threshold. Violent nightmares may occur; in the author's experience, some patients have fewer of these on *rescinnamine* than on *reserpine* Partial or total loss of libido in the male is a common problem. A few cases resembling paralysis agitans have been noted in association with rauwolfia, as well as with other tranquilizers such as chlorpromazine. Weight gain is common, and in some cases of heart failure has been said to be associated with worsening of the edema

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Emphasis on the side actions of rauwolfia should not detract from the use of these remarkable therapeutic agents for sedation and moderate hypotension. The drugs have been claimed to be most effective in young hypertensive patients with labile blood pressu anxiety, tachycardia, and no evidence of v cular disease. Yet, there is often a satisfyi response of blood pressure and symptoms headache, dizziness, insomnia, and nervo ness in older persons with "fixed" hypertens associated with evidence of vascular disea

DOSAGE. Orally, the pure alkaloids are gi in daily doses of 0 25 to 1.0 mg for 7 to days, after which the daily dose is reduced 0.1 to 0.25 mg, depending on the respon Parenteral administration (1 to 2.5 mg int venously or intramuscularly) has the same g eral effects as the oral, causing sedation an moderate blood pressure fall lasting about 6 Curiously, in some individuals it may take s eral weeks for the full hypotensive effect to pear; when the drug is discontinued, its eff may last 1 to 4 weeks, even though the adm istered drug appears to be excreted in sev hours Undesirable side effects are often c trolled by omitting the drug for 1 week of 4. The hypotensive effect can be succ fully overcome by ephedrine or phenylephr Synergistic effects with other hypoten drugs are difficult to prove, but the brady dia of rauwolfia tends to overcome the tac cardia of hydralazine, its bowel-stimulating tion may mitigate the constipation from gan onic blocking drugs, and its tranquilizing fects may make veratrum effective with vomiting Thus, smaller doses of the o drugs can usually be used if rauwolfia is employed Rauwolfia and its pure alkal therefore seem to be worthwhile in early, r cases if nervousness and tachycardia are pro nent, and simple barbiturate sedation or p chotherapy ineffective In more severe c with headache, dizziness, or other evidenc hypertensive cardiovascular disease, it may useful alone but more likely in combina with other drugs. The most serious side ef is depression

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synthetic agent were first described in 1950. *Hydralazine* is an orally effective drug which appears to act on the central nervous system as well as peripherally, where it neutralizes the effects of a number of circulating vasopressor agents. In animals, sympatholytic activity is demonstrable, with the doses used in man, these effects are minimal. Although an increase in renal blood flow accompanies the moderate fall in systolic and diastolic pressure, this drug is not more effective in renal hypertension than in other varieties. It does not increase glomerular filtration rate and does not elevate to normal the depressed renal blood flow of essential hypertension. A direct stimulating effect on the heart results in tachycardia and increased cardiac output, which explains the aggravation of precordial pain and of congestive heart failure which has sometimes occurred even when blood pressure was lowered by this drug. Hydralazine may improve the contours of the ballistocardiogram, presumably because of peripheral vasodilatation, however, the electrocardiogram in patients with coronary disease may show changes of hypoxia after hydralazine. For these reasons, *rauwolfia* or *veratrum* should be used to slow the heart rate and lower the blood pressure before hydralazine is given to patients with coronary artery disease or congestive failure. Similarly, if the pressure is first lowered with a ganglionic blocking drug, hydralazine can then be given cautiously to such patients.

Toxic symptoms include nausea, vomiting, some degree of postural hypotension, and headache. The latter may be quite severe but can usually be minimized if treatment is begun with small doses. Prolonged administration of the drug has resulted in fever, edema, rashes, and a new type of disorder resembling certain collagen diseases. As many as 10 per cent of patients who receive this drug in large doses and for more than one year develop some or all of the syndrome. Fully developed, it includes arthritis, rash, fever, anemia, hematuria, lymphadenopathy and splenomegaly, albuminuria, positive cephalin flocculation, and even lupus erythematosus cells. This syndrome has appeared primarily in patients receiving large doses (over 500 mg daily) and in whom the blood pressure was successfully lowered. Thus far the disturbance has remitted when hydralazine was stopped, and in some cases corticotropin given. Rarely hydralazine has been observed to cause acute psychotic reactions.

Initial dose should be 25 mg or less, four times daily. Increments of 25 mg per dose are added every 3 to 4 days unless severe headache appears. Daily doses have ranged as high as 500 to 600 mg a day, but in view of the high incidence of drug toxicity, it is doubtful whether more than 400 mg a day should be given. Prolonged administration of hydralazine alone is accompanied not only by a rising incidence of drug toxicity but also by a diminution in the number of good responses. Initially, satisfactory hypotension is obtained in about one-third of the patients, but after 1 to 2 years of treatment the percentage of patients showing good results has diminished to one-tenth. Milder forms of hypertensive disease may respond to small doses of *hydralazine*, especially in conjunction with *rauwolfia* or *veratrum*, without a high incidence of toxic reactions. In general, large doses of hydralazine should be reserved for patients with severe forms of hypertensive disease in whom other treatment is inadequate. In conjunction with *hexamethonium*, however, it has been a very effective agent in severe forms of hypertensive disease.

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Hydralazine (1-Hydrazinophthalazine, Apresoline). The hypotensive properties of this

theoretically less of a problem However, some instances of central nervous system disturbance, tremors, and hallucinations, usually in very sick patients, have been attributed to it.

Dosage for each patient is a matter of trial. Pentolinium is administered in doses of 20 mg (of the bitartrate salt) after breakfast, in midafternoon, and at bedtime. Increments of 20 mg are made slowly every few days until either satisfactory blood pressure response (not lower than 120 mm Hg systolic in the erect position) or uncontrollable toxic effect appears Mecamylamine is begun in doses of 2.5 mg—in three daily doses, as with pentolinium Increments are 2.5 mg Ecolid is begun in two daily doses of 50 mg each, with increments of 25 to 50 mg every few days.

Many investigators, following Ayman's suggestion, recommend home blood pressure readings, to obviate the notoriously unreliable "office" reading, and adjustment of medication dosage on the basis of home blood pressures[2] Some believe that transient dizziness in the erect position is a satisfactory end point. In general, smaller doses are required for patients who are active than for those in bed. Alcohol, vigorous exercise, hot weather, a large meal, low-salt diet, previous sympathectomy, all tend to potentiate orthostatic hypotension. Education of the patient to understand the effects and side effects of these drugs is essential to good management

Contraindications to ganglionic blocking drugs include (1) generalized and, especially, advanced cerebral arteriosclerosis, (2) prostatic symptoms, (3) recent (6 to 12 weeks) coronary or cerebral thrombosis, (4) pyloric stenosis, (5) uremia, and (6) noncooperation by the patient Recently Schroeder has pointed out that some patients with moderate degrees of nitrogen retention can be successfully treated. Although nitrogen retention may increase during the early period of therapy, persistence may result in a subsequent fall of the blood urea level Therapy with ganglionic blocking drugs is indicated in patients with the malignant phase of hypertension, with congestive failure or other evidence of severe hypertensive disease, preferably with rauwolfia and hydralazine, if simpler measures have been ineffective Any patient recommended for sympathectomy should have prior therapy with ganglionic blockers.

[2] The entire dose is taken if the standing systolic pressure is 140 or over, two-thirds is taken for systolic pressure between 120 and 140, the dose is omitted if the systolic pressure is under 120 mm Hg.

Choice of Drug Combinations. The empirical nature of therapy in hypertensive cardiovascular disease has naturally led to the use of several drugs or measures in combination. The undesirable effects of some of the drugs are mitigated by the smaller doses necessary and because some of the side effects tend to overcome each other (such as bowel disturbance with ganglionic block and rauwolfia). However, combinations leave the patient vulnerable to additional toxic reactions The more potent drugs seem to be more toxic, but serious side effects may appear with any of them

Reassurance, supportive *psychotherapy*, and *reorientation* to the stresses of life are usually all that is necessary for the patients with mild, early, asymptomatic hypertension and no evidence of vascular disease, and for those whose hypertension has proved benign by its long duration (especially elderly persons with only moderate degrees of left ventricular enlargement). *Phenobarbital* may be helpful in this group *Rauwolfia*, especially if used intermittently with close observation for side effects, may be useful in these patients if they are very tense Hypotensive agents should be given to patients with sustained high diastolic pressure, especially men, and to patients with evidence of progressive, but not malignant, hypertensive disease. Initial therapy should include *rauwolfia* or *low-sodium diet*. If there is no response in 2 to 3 months, *veratrum* (or *protoveratrine*) may be tried Later, if the disease remains uncontrolled, this group may require *ganglionic blocking drugs*. Patients with hypertensive cerebrovascular disease may be given *rauwolfia, low-sodium diet, veratrum*, or small doses of *hydralazine* in that order. Hypertension and coronary artery disease may be treated with *rauwolfia, low-sodium diet*, and *veratrum* *Ganglionic blocking drugs* cautiously administered to lower pressure slowly and not too far, with the later addition of small doses of *hydralazine*, occasionally give remarkable relief of angina If congestive failure or the malignant phase unresponsive to salt restriction or veratrum appears, *ganglionic blocking drugs* must be given. For acute hypertensive crisis,

function. The end organs of both the parasympathetic and the sympathetic system remain responsive to the appropriate chemical stimulus, or to a postganglionic electrical stimulus. For example, arterioles, unresponsive to preganglionic stimulation after ganglionic blockade, will constrict to norepinephrine; the salivary gland, unresponsive to the stimulus of food, will secrete if a cholinergic drug is given, similarly, the lax bowel will constrict with Prostigmine or other cholinergic agents.

In general, the effects of these drugs are those to be expected from a blockade of autonomic ganglia. Most patients, even normotensive persons, show *orthostatic hypotension* and *compensatory tachycardia* after administration of ganglionic blocking drugs Blood pools in the legs and splanchnic region unopposed by reflex sympathetic vasoconstriction of arterioles and veins. When severe, this may lead to *faintness* or even *collapse* If the patient sits or lies flat, such symptoms should abate. Since the aim of treatment is to achieve *some* degree of postural hypotension, this cannot be considered a side effect In some instances, there is even decline of the supine blood pressure The venous pressure falls in normal persons as well as in those with congestive failure If the subject is immersed in a swimming pool, the external pressure of the water replaces sympathetic vasoconstriction of venous channels and hence the hypotension and tachycardia are completely counteracted

As with other hypotensive agents, the hypotension produced by ganglionic blocking drugs does not materially interfere with adequate renal function, but poor renal function is apt to be adversely affected Interference with sympathetic nervous activity causes an increased susceptibility to other stresses Less anesthesia is required for patients under ganglionic block; hypoglycemia may progress quietly into coma without eliciting any of the epinephrine-like reaction characteristic of hypoglycemia in the normal person In warm weather, body temperature rises because of inhibition of sweating, in cold weather, the patient shivers because of lack of reflex skin vasoconstriction Impotence is common but yields to omission of the medication.

Parasympathetic activity is also blocked by these drugs, causing additional undesirable side effects. There is interference with the pupillary reactions to light and accommodation, causing intolerance to bright sunlight and blurred vision. Decreased salivation causes dryness of the mouth. Secretion of hydrochloric acid by the stomach, in the resting state and after insulin, is inhibited, and both stomach and small intestine empty more slowly. The gastric effects of the drug are less pronounced if the stomach is full Although nausea is fairly common, diarrhea is rare Decrease in intestinal motility causes constipation and, in some cases, even ileus. Urinary retention in the male with prostatic hypertrophy may be a problem. Since the oral dose is so much larger than the parenteral one (except for mecamylamine), constipation favors excessive absorption of the drug from the gut and toxic reactions such as paralytic ileus or profound hypotension. Daily bowel evacuation is very important. Deaths have been reported from paralytic ileus as well as from cerebral or coronary thrombosis secondary to severe hypotension. The important differential diagnosis between paralytic ileus and mesenteric thrombosis can be made by noting loss of the pupillary reaction to light and dryness of the skin despite severe hypotension. The side effects due to interference with parasympathetic activity are remedied by oral cholinergic drugs such as *pilocarpine* (5 mg), *Prostigmine* (15 to 30 mg), and urethan of β-methylcholine (*Urecholine*) (5 to 20 mg).

Fatal pulmonary fibrosis has been reported in a small number of patients who received large doses of hexamethonium. These were very sick individuals, many of them in the malignant phase, who also received hydralazine This complication, which appears to be more common in the Negro, has not been reported with other ganglionic blocking drugs. In 9 out of 44 patients with hypertension who died after treatment with hexamethonium or pentolinium, dissecting aneurysm of the aorta was found at post mortem. This high incidence suggests that this also may be an untoward result of therapy

Pentolinium is more potent than hexamethonium on a weight basis and has a longer duration of action, which is its major advantage *Ecolid* has a still longer duration of action and can usually be given in two daily doses *Mecamylamine* is absorbed so well from the gastrointestinal tract that overdosage is

9

Experimental hypertension

JUAN CARLOS FASCIOLO

PRINCIPLES OF HEMODYNAMICS

The pressure to which the blood is subjected within the arteries depends on the elastic tension of their walls. This tension increases as the elastic fibers are distended, as occurs upon increase of the volume of blood that fills them. The relationship $\frac{\Delta PA}{\Delta VA}$, change in (intra-arterial) pressure (ΔPA) caused by change in (intra-arterial) volume (ΔVA), is a function of the *capacity* and *distensibility* of the arterial system.

The "arterial capacity" may be defined as the volume that fills the arterial system when the internal pressure equals the external pressure. The distensibility may be expressed in terms of arterial "compliance," which could be defined as the change in arterial volume produced by each millimeter of mercury of difference in transarterial pressure,

$$C = \frac{\Delta VA}{\Delta P \text{ mm Hg}}$$

This compliance will be in inverse proportion to the rigidity of the vessels. Changes in the capacity of the arterial system modify the value $\frac{\Delta PA}{\Delta VA}$. If the capacity increases, the value of the relationship decreases, and vice versa. The changes of compliance have the same effect. When the latter increases, the value of $\frac{\Delta PA}{\Delta VA}$ decreases, and when C decreases (i.e., the vessels become more rigid), the value increases. In the arterial system, the capacity and compliance depend upon the characteristics of the larger vessels, especially of the aorta. Therefore the arterial system of a subject in whom the capacity and compliance of the arteries have a constant value should be considered without admitting the possibility that both compliance and capacity may be changed by variations in the tone of smooth muscle present in the walls of the larger arterial vessels. In this case the value of PA will be a function of VA. VA in turn depends on the balance between *the amount of blood entering the system in a certain period of time—Ve (ventricular ejection)—and that amount which leaves the system—Vs.*

$$VA = Vi + (Ve - Vs)$$

where Vi (initial volume) = the volume present before the time in which Ve and Vs are measured.

Ve is dependent upon the venous return and the physiologic status of the heart. Vs depends upon (1) the difference in pressure between the arterial and venous systems; (2) the viscosity of the blood; and (3) the diameter and length of the smaller blood vessels, especially the arterioles. If the last two factors are designated as R, Poiseuille's law states that $PA = Ve \times R$.[1] Poiseuille's law is applied to systems in which viscous fluids circulate without turbulence. It appears that in the arterial system, blood, because of its cellular components, behaves in the smaller vessels as a pseudoplastic fluid, while turbulence seems absent. For this reason, the formula $PA = Ve \times R$, which

[1] The most important formulas pertaining to the cardiovascular system can be found in Part II, Chaps. 6, 14, 15, and 16. *Editor.*

veratrum is the drug of choice. Parenteral *reserpine* may be a useful adjunct. Ganglionic blocking drugs have been used effectively, but are less easily controlled. One-half or more of the patients in the malignant phase of hypertension can now expect reversal if uremia is absent, with various drugs, singly and in combination. The ganglionic blocking drugs are most widely used for this purpose. In this condition particularly, hypotensive medication should not be withdrawn abruptly, lest heart failure, cerebral hemorrhage, or irreversible uremia be precipitated.

SURGERY

The dietary and drug treatment of hypertension is not always effective, and for some severely ill patients it may be necessary to recommend surgery on the sympathetic nervous system or adrenal glands No patient should have surgery without a prior trial of drugs, including ganglionic blockers The popularity of sympathectomy has been declining, even though it was the first procedure clearly to improve the prognosis in malignant hypertension. The application of sympathetic nerve surgery is as empirical as drug treatment, and it is impossible to select the patients destined to do well with operation

The variety of surgical procedures recommended has extended to virtually total sympathectomy, representing formidable and multiple operations, and most surgeons do not believe this offers more benefit than the less extensive procedures. The most widely used operations are those of Peet and of Smithwick. The former is often done in one stage; it does not entail prolonged morbidity from postural hypotension and does not interfere with ejaculation.

The sympathetic chain, from the sixth to the twelfth thoracic nerve, including the splanchnic nerves, is resected on both sides Portions of two ribs must be removed, and the operative mortality is 3 per cent. The Smithwick procedure includes the lumbar ganglia, thus resulting in postural hypotension and interference with potency. This procedure has the advantage of exposing the adrenal glands (to detect a rare instance of pheochromocytoma) as well as the kidneys. Both the Smithwick and Peet procedures may cause severe persistent postoperative neuritis. There is disagreement concerning the necessity of postural hypotension for a good therapeutic response with improvement in survival rates. Lowered blood pressure should persist for a year before the operation can be considered successful.

While the exact role of sympathetic surgery remains unsettled, such operations having been displaced to a large extent by ganglionic blocking drugs, there are a few situations in which operation should be recommended. Any patient with malignant hypertension not responsive to medical treatment within 2 months should have sympathectomy if nitrogen retention is absent. *Surgery is invariably unsuccessful when nitrogen retention is present.* Sympathectomy should be advised for patients with evidence of the rapidly progressive but not necessarily malignant phase of hypertension who cannot be followed very closely, live far from good medical attention, lack the intelligence and cooperation necessary in using the more potent hypotensive drugs, or have not responded to medical treatment Apparently, sympathectomy increases the later effectiveness of drugs and diets.

Adrenalectomy, with or without accompanying splanchnic resection, is still an experimental procedure The good results reported can often be equaled by sympathectomy alone or with sodium restriction In such patients, strict low-sodium intake, with additional measures if necessary to cause negative sodium balance (mercury, resins), and ganglionic blocking drugs would be equally effective. Adrenalectomy is rarely successful unless sufficient adrenal tissue is removed so that the patient requires replacement steroids. Even with total adrenalectomy, some patients show simultaneously high blood pressure and the serum chemical derangements of adrenal insufficiency, not to mention the hazards of cortisone psychosis and metabolic accidents

The variety of empirical medical treatments and the radical nature of the surgery recommended in hypertensive disease indicate that management is far from ideal Difficulties in prognosticating for the individual patient and weighing prognosis against the dangers and discomfort from treatment compound the physician's problem. Yet there is growing agreement that these measures, to be successful, must lower the blood pressure. There is mounting evidence for the suggestion that maintenance of lowered blood pressure will prevent the serious sequelae of this disorder.

sure without changes of the femoral pressure. The increase in carotid pressure is not immediate. If the narrowing is done below the renal arteries, no carotid hypertension occurs. This fact, which has been confirmed in other species, led to the theory which explains the hypertension as the result of renal ischemia caused by the narrowing of the aorta. It has also been shown that compression of the aorta above the renal arteries increases the diastolic pressure, not only in the carotid but also in the femoral arteries. This seems to indicate a generalized vasoconstriction, which in turn could be explained by a humoral mechanism. Nevertheless a mechanical factor also plays a role. This was demonstrated by compressing the thoracic aorta in experiments producing acute arterial hypertension.

On account of the rapid development of collateral circulation, constriction of the aortic arch in the dog does not easily elicit a permanent hypertension (Page, 1940).

Renal Hypertension. It is possible to produce hypertension by altering the renal function by various methods. The degree and duration of the hypertension depend upon the method used, it is often mild and brief. None of the methods described prior to the study of Goldblatt et al. (1934) dealing with incomplete renal ischemia was capable of inducing permanent hypertension with the regularity necessary for systematic study. Most of the methods employed for eliciting renal hypertension are given in the following list

1. Nephrotoxic substances (uranium, bismuth, mercurial and lead salts, oxalates, streptococcic toxins)
2. Nephrotoxic serum
3. Surgical reduction of the renal parenchyma
4. Ligation of the renal arteries or their branches
5. Renal embolism
6. Roentgen irradiation
7. Renal vein occlusion
8. Intermittent occlusion of renal pedicle
9. Occlusion of the ureters
10. Continuous stimulation of the renal nerves
11. Renal compression and perinephritis
12. Total nephrectomy
13. Incomplete renal ischemia
14. Renal lesions caused by choline or potassium deficiency

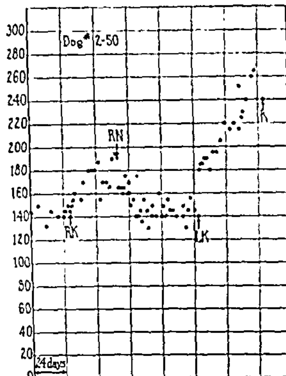


Fig. 12-7. Effect of renal ischemia on the arterial pressure of the dog. Mean arterial pressure in millimeters of mercury. RK, moderate compression of the right renal artery, RN, right nephrectomy; LK, intensive constriction of the left renal artery; K, sacrificed. (From Goldblatt, Ann. Int. Med., 1937.)

Renal Ischemia. The classic experiments of Goldblatt et al. showed that incomplete renal ischemia, secondary to narrowing of the renal artery, is followed in the dog by a permanent elevation of the arterial pressure (Fig. 12-7). These results have been repeatedly confirmed in several other species, such as *Macacus*, rabbit, cat, goat, rat, etc. Goldblatt's original method consisted of placing a silver clamp on the renal artery (Goldblatt clamp), so that the degree of renal ischemia could be regulated.

In the dog, unilateral ischemia (i.e., the other kidney is left intact) is followed by hypertension of 2 to 4 weeks' duration. If the ischemia is bilateral (i.e., if one kidney is ischemic and the other has been removed), the hypertension usually becomes permanent. However, even then, the blood pressure may subsequently decrease and even become normal. This is the result of an increase in collateral circulation; if the new vessels are tied, hypertension again develops.

If the compression is removed from the renal

TABLE 12-4. METHODS EMPLOYED TO PRODUCE ARTERIAL HYPERTENSION

Reduction of the caliber of the aorta	Thoracic aorta or abdominal aorta (above the origin of the renal arteries).
Renal hypertension	Partial or total nephrectomy, renal ischemia, perinephritis; renal vein constriction, etc
Adrenal hypertension	*By means of DOCA* (in the rat) Connected to the sodium content of the diet; potentiated by partial nephrectomy. *By means of cortisone* (in the rat) Sodium is not necessary; potentiated by partial nephrectomy. *By means of aldosterone* Doubtful action *Regeneration of the adrenal cortex* It is necessary to associate reduction of the renal mass and sodium administration
Hypertension by steroids	By vitamin D, corticosterone, methyl-androsternediol, and fluorine derivatives of cortisone (in dogs and rats)
Pituitary hypertension	*By means of somatotropin*, potentiated in the rat by a reduction of the renal mass *By means of ACTH* (in rats) *By thyrotropin* (in the rat), associated with renal mass reduction, the presence of the thyroid is necessary
Thyroid hypertension	*By means of thyroid administration associated with renal mass reduction* (in rats)
Increase of intracranial pressure	Acute and chronic hypertension (in dogs and rats)
Section of the carotid and aortic nerves	Chronic hypertension (in dogs and rabbits)
Cerebral ischemia	Chronic hypertension (in dogs and rabbits)
Semidecortication	Chronic hypertension (in rats)

should be considered as only approximate when applied to the vascular system, is still useful because it makes it possible to deduce the direction of changes that occur in *PA* when *Ve* or *R* is modified.

In most cases of clinical or experimental arterial hypertension, there are no changes in *Ve* nor in viscosity. *Therefore, the increase in pressure is the result of an increase in peripheral resistance.* It is evident that the cause of hypertension should be sought in an increase of tone of the arteriolar muscles, and that knowledge of the humoral, neurogenic, or other factors that modify this tonus will be the key to our knowledge of hypertension.

EXPERIMENTAL PRODUCTION OF ARTERIAL HYPERTENSION

The mechanisms capable of producing arterial hypertension may be conveniently studied by reviewing the different procedures that have been used to produce chronic hypertension in animals. Table 12-4 summarizes the most important methods and some of their characteristics.

Aortic Compression. Narrowing of the thoracic aorta produces an increase in the arterial pressure in the arteries arising above the point of constriction. The narrowing increases the resistance *R* to blood flow; then if the cardiac output remains constant, there is an increase in pressure which is proportional to the resistance ($PA = Ve \times R$).

The aorta has been experimentally narrowed at different levels (Fig. 12-6). Goldblatt et al (1939) showed that in the dog, constriction of the abdominal aorta above the renal arteries causes a permanent increase in carotid pres-

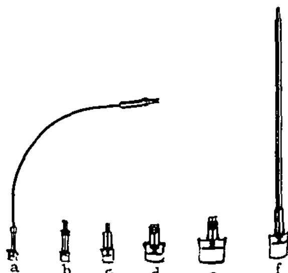


Fig 12-6. Various types of clamps for the compression of aorta or renal arteries. *a*, Clamp with flexible wire for external constriction *b*, *c*, *d*, and *e* Several types of clamps to be left in the animal *f*. Clamp for the constriction of the aorta from the outside. (From Goldblatt. Am J. Clin. Path. 1940)

plasma volume is usually diminished, but normal values may be found, indicating either that the increase of aortic pressure is sufficient to compensate for the narrowing of the renal artery or that the intrarenal resistance has decreased. The filtration is normal and, therefore, there is no nitrogen retention If the blood flow is decreased, the filtration is maintained, because of an increase of the filtration fraction, possibly caused by constriction of the glomerular efferent arteriole. There is no hematuria, proteinuria, or cylindruria, and the concentration and volume of the urine are usually within normal limits.

In this group, the structural changes found in the kidney and cardiovascular system are insignificant. If the hypertension has a certain duration, there is a moderate cardiac hypertrophy, but there are no alterations in the large vessels and the thickness of the aortic wall is normal Usually there is thickening of the muscular layers of the arterioles. The ischemic kidney is normal or shows a slight atrophy of the tubules Alterations of the juxtaglomerular apparatus have been described.

Malignant Hypertension. If both renal arteries (or one renal artery in an animal with only one kidney) are severely constricted, in addition to arterial hypertension, insufficiency of the excretory function of the kidney develops, and retention of urea, nonprotein nitrogen, and creatinine occurs. There is a decrease of the clearance function, and some animals present an acute hypertension, associated with convulsions and retinal detachment produced by retroretinal exudates and hemorrhages Later on, hemorrhagic vomitus and diarrhea may occur On *autopsy, petechiae and hemorrhages* are noted in various organs, especially in the intestines, stomach, and pancreas and serous effusions in the peritoneum and pericardium Microscopically, hyalinization and necrosis of the arteriolar walls are seen. The hyalinization is characterized by deposits of hyaline material in the subendothelial layers, with partial or total obliteration of the lumen. The necrosis may extend through the entire arteriolar wall and cause hemorrhages These arterial lesions seem to be due to the combination of hypertension and renal insufficiency. The areas protected from an increase of pressure by narrowing of the vascular lumen do not exhibit the typical lesions of malignant hypertension (Goldblatt, 1938). In the hypertension of rats caused by daily injection of Doca, carotid ligation prevents the development of cerebral lesions.

The aorta has been experimentally constricted at various levels. Goldblatt et al. (1939) showed that in the dog, constriction of the abdominal aorta above the renal arteries causes a permanent increase of carotid pressure without modification of the femoral pressure. When both carotids are ligated, the protection of the cerebral circulation is complete; it is limited to the homolateral side, when the ligation is unilateral (Robert, 1950).

The possibility of an absorption of autolytic renal proteins has been considered as the cause of vascular lesions.

Protective Action of the Normal Kidney. The increase of blood pressure due to unilateral renal ischemia in the dog is transitory and usually moderate if the other kidney is intact. The extirpation of this kidney is followed by a rapid increase of blood pressure, which then becomes permanent (Fasciolo, 1938). Therefore, it is likely that the normal renal tissue is able to neutralize, within certain limits, the hypertensive effect of the ischemic tissue. The mechanism of this protective effect is unknown. Some investigators think that the hypertrophied normal kidney takes over part of the work that should be done by the ischemic kidney, thus overcoming the metabolic disturbance that causes hypertension. Other data, such as the increased sensitivity to the pressor action of renin, found in nephrectomized animals, suggest a humoral mechanism. The removal of both kidneys in the dog and rat is followed by arterial hypertension if survival is made possible, suggesting a normotensive action of the healthy kidney tissue. This point will be discussed further.

Mechanism of the Hypertension Caused by Renal Ischemia. In the dog made hypertensive by renal ischemia, cardiac output, blood volume, and blood viscosity are normal. For this reason, the arterial hypertension should be attributed to an increase of peripheral resistance The latter is probably secondary to an increase of arteriolar muscular tone. As this tone may be modified by either humoral or neurogenic mechanisms, this form of arterial hypertension may be attributed to either of these mechanisms However, the blood pressure of hypertensive dogs is not normalized, nor is the increased pressure caused by ische-

artery or if the ischemic kidney is removed (in the experiments in which the other kidney is normal), *the arterial pressure again becomes* normal. In other species, such as the rat, unilateral perinephritis may cause a permanent hypertension and the removal of the diseased kidney fails to normalize the arterial pressure (Fig. 12-8). This is apparently because of secondary changes produced in the undamaged kidney by the hypertension.

In arterial hypertension of the dog, produced by renal ischemia, there is an increase of both systolic and diastolic pressures. The heart rate and the cardiac output as well as the blood volume are normal. The degree of alteration of renal function depends on the degree of renal ischemia. If the compression *of the renal arteries is moderate, it is possible* to obtain chronic arterial hypertension without renal insufficiency.

Renal ischemia in the dog may be followed by two types of hypertensive disease: (1) *benign arterial hypertension* without renal or vascular changes, (2) *malignant arterial hypertension* with multiple vascular lesions and renal insufficiency.

Benign Hypertension Induced by Renal Ischemia. When the reduction of the lumen of the renal arteries is moderate, the excretory function of the kidney is not altered. The renal

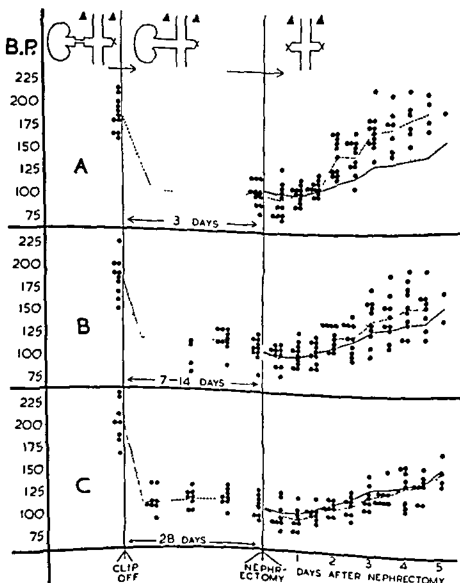


Fig. 12-8. Effect of renal ischemia and of nephrectomy on blood pressure of the rat. A. Nephrectomy at the third day from the elimination of the clip B After 14 days. C. After 28 days. Dotted line, average from ischemic group; full line, average of normal rats after double nephrectomy. (From Floyer. *Clin. Sci.* 1955)

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Fig. 12-9. Pressor action of renin and angiotensin. Arterial pressure of anesthetized dogs in millimeters of mercury; time in minutes. Above: The arrow indicates the moment in which the circulation was reestablished in a kidney after 6 hr of complete ischemia. Effect of liberation of renin. Center: 1. 20 ml horse serum plus 0.5 ml of a renin solution separately incubated, then mixed and precipitated with alcohol. 2. Same as in (1) but horse serum and renin solution incubated together 15 min at 37°C. 3. As in (1) but with bovine serum. 4. As in (2) but with bovine serum. Below: Intravenous injection of angiotensin at a rate of 1 unit per minute. 1. Beginning of injection. 2. End of injection. (From Braun-Menéndez et al. *Hipertensión arterial nefrogena.* El Ateneo, Buenos Aires, 1943.)

mia prevented, by renal denervation, sympathectomy, or the destruction of the anterior roots; nor does spinal destruction prevent the increase of pressure. One is therefore inclined to conclude that the increase of arteriolar tone is due to a humoral mechanism.

THE HUMORAL MECHANISM. The arteriolar muscular tone could be stimulated by either an increase of vasopressor or a decrease of vasodepressor substances in the blood. The reactivity of the tissues to vasoactive substances could also be modified, but this modification could only be secondary to changes in the composition of the medium or of the muscle itself (content of sodium, potassium, or other substances). In the last analysis humoral modification would still be involved.

Renal insufficiency and the secondary retention of various metabolites are unable to cause hypertension. Renal ischemia, on the other hand, can elicit hypertension without causing changes of the renal excretory function. Moreover, unilateral renal ischemia is followed by high blood pressure and the removal of the ischemic kidney is rapidly followed by normalization of the blood pressure level. These facts indicate that the vasoconstriction responsible for the hypertension is due to some factor that the ischemic kidney pours into the circulatory system.

RENAL PRESSOR SYSTEM.[2] Tigerstedt and Bergman (1898) showed that the normal kidney contains a hypertensive substance, *renin*. This substance, injected into the blood stream, causes, after a short latent period, an elevation of blood pressure that may persist for 30 to 40 min if large doses are employed. The pressor action is independent of the nervous system and is due to direct action on the arterioles (Fig. 12-9).

Renin is a protein, and its activity is rapidly destroyed by heat over 60°C. It is found in the renal cortex and can be purified by precipitation with ammonium sulfate, sodium chloride, and other chemicals.

The pressor activity of renin is powerful. The most purified preparation has a pressor activity of 470 units per milligram (Haas et al., 1953). A *pressor unit* is the amount of renin that causes an increase of 30 mm Hg in the arterial pressure of a 10-kg dog. Renin has no direct pressor action. It acts on a plasma protein, giving origin to a true pressor substance, *angiotensin*.[3] The plasma protein necessary for the formation of angiotensin has been called "angiotensinogen." It is a protein formed in the liver and is an alpha-$_2$ globulin. Renin acts as an enzyme, angiotensinogen is the substrate. The product of this reaction is a polypeptide with vasoconstrictive action—angiotensin. Applying pepsin on angiotensinogen causes the liberation of a polypeptide which is similar to angiotensin (*Croxatto and Crox-*

[2] See also Part 2, Chap. 27. *Editor.*

[3] Braun-Menéndez, Fasciolo, Leloir, and Muñoz (1939) called the substance formed by the action of renin on the plasma "hypertensin", Page and Helmer (1940) called the same substance "angiotonin." More recently, an international agreement has combined the two names, creating "angiotensin."

Angiotensin is destroyed by a peptidase, called *angiotensinase*, present in the plasma. This enzyme is found in greater amount in several tissues, particularly the kidney, spleen, and liver. The red blood cells contain an appreciable amount of it The production and destruction of angiotensin seem to occur as follows.


Renin + angiotensinogen → angiotensin + x


Angiotensin + angiotensinase → inactive product

The amount of angiotensinogen contained in the plasma varies slightly in the different species but is around one unit for each 2 or 3 ml plasma One unit is the amount that forms an angiotensin unit, i e, one able to increase by 30 mm Hg the arterial pressure of a dog weighing 10 kg, anesthetized with chloralose It is clear that the total amount of angiotensinogen present in the blood can produce a considerable amount of angiotensin Moreover, angiotensinogen is continuously produced by the liver In effect, if all the angiotensinogen of the plasma were transformed after injection of a large dose of renin, it would be totally replaced in about 2 to 3 hr. The *renin of the various species presents certain differences* (Fasciolo et al, 1940) That of a pig is able to form angiotensin with the angiotensinogen of the pig, dog, rat, rabbit, etc Human angiotensinogen, however, forms angiotensin with renin of man, monkey, or ox, but not with that of other species This is important because

eign renin but also the animal's own renin (Wakerlin and Johnson, 1941)

Angiotensin The pressor action of angiotensin lasts only from 3 to 5 min, because it is rapidly destroyed in the blood and tissues. If angiotensin is *injected* by a continuous intravenous drip, *the* pressor effect persists during the whole time of the infusion. The prolonged action of renin is due to its slow destruction while angiotensin is produced

The study of the chemical *structure* of angiotensin has shown that it is a polypeptide; the number and *relationship* of the aminoacids it contains have been identified (Edman, 1945, Skeggs et al., 1955–1956, Peart et al., 1957). Angiotensin has been synthesized independently by two different groups (Bumpus et al., 1957; Rittel et al., 1957). According to Skeggs et al. (1954), the action of renin over angiotensinogen would create a decapeptide (angiotensin I). A conversion enzyme present in the plasma would remove two amino acids from angiotensin I, transforming it into an octapeptide (angiotensin II). According to Helmer (1954), only angiotensin II acts over the vascular musculature, but if angiotensin I is injected, it would be immediately converted in the blood to angiotensin II, having a vascular action.

The Renal Pressor System in the Hypertension Caused by Renal Ischemias. Houssay and *Fasciolo* (1937) grafted ischemic kidneys of *dogs with recent hypertension* in the neck of nephrectomized dogs, connecting the artery and vein of the kidney respectively to the carotid and jugular vein of the recipient animal. *This graft* was followed by a prolonged increase of arterial pressure in the recipient. Grafting of a normal kidney fails to elicit this action.

The substance responsible for this increase has characteristics similar to those of renin.

An increase in the plasma content of renin during the early stages of hypertension has been ascertained through the bioassay method developed by Leloir et al. (1940) and later *modified*. However, later stages do not reveal the same increase of renin even though the *pressure* remains elevated or even gradually increases It is evident that if renin is the agent responsible for the initial increase of pressure that follows renal ischemia, another agent or mechanism maintains the hypertension in later stages Theoretically, angiotensin could be *formed* within the ischemic kidney. If that were the case, renin would not be found in increased amount in the plasma *even though* the increase of angiotensin could be responsible for the hypertension.

The investigations of Skeggs et al (1951) seem to indicate that in the hypertension caused by renal ischemia, the blood of the dogs operated upon contains a greater amount of angiotensin, which would be responsible for the vasoconstriction and hypertension

The following facts *show* the role of the renal pressor mechanism in the hypertension following renal ischemia:

1. The blood concentration of angiotensin is increased. The studies of Skeggs et al. seem to show that the increase is moderate, though sufficient to maintain the elevated blood pressure. However, Scornick and Paludin (1961) could not confirm this, at least in benign hypertension.

2. Renal ischemia produces secretion of renin. Blood renin increases in the initial periods of hypertension but not in the subsequent stages.

3. The pressor action of renin and angiotensin has hemodynamic characteristics similar to that found in the hypertensive animal. There is diffuse vasoconstriction, and the increase of blood pressure is not inhibited by either sympatholytics or sympathectomy There are no modifications of the pulse rate or cardiac output.

4. A continuous intravenous infusion of renin causes a lasting hypertension in the rabbit This is not obtained with other pressor substances.

5. The heterologous injection of renin or the administration of antirenin serum neutralizes the pressor effect of renin and has a hypotensive effect in the hypertensive dog, both in the acute and in the chronic stages. The role of the renin-angiotensin system in the production of renal hypertension seems reasonably well established. This does not mean that other factors cannot contribute to the production or maintenance of hypertension Changes in reactivity of the arterioles to vasoconstrictor substances normally contained in the blood could play a certain role The experimental data are not always consistent, but it seems that vascular reactivity to epinephrine, norepinephrine, renin, and pitressin is somewhat increased in renal hypertension. However, the interpretation of these experimental results is difficult because of the different tension levels above which the increase is measured. Some authors have attributed the hypertension to other vasoconstrictor substances, such as tyramine, guanidine, 5-hydroxytryptamine, or other pressor substances However, evidence in favor of this hypothesis is insufficient

THE ROLE OF THE ENDOCRINE GLANDS The removal of the pituitary gland in the dog decreases the hypertension caused by renal ischemia (Page and Sweet, 1937) without, however, bringing the blood pressure to a normal level.

Compression of the renal arteries in animals deprived of the pituitary gland is followed by an increase of blood pressure.

The action of the pituitary gland is in the anterior lobe and is possibly mediated through the adrenal cortex. Extirpation of the cortical part of both adrenal glands is followed by a fall of blood pressure in the dog with hypertension caused by renal ischemia. The administration of adrenal steroids and adrenal extracts again increases the blood pressure but the previous level is not reached (Goldblatt, 1937). Similar results have been obtained in the hypertension of the rat caused by experimental perinephritis. The other endocrine glands seem not to play an important role in arterial hypertension caused by renal ischemia in the dog, as can be demonstrated by the effect of their removal in the hypertensive animal. However, in the partially nephrectomized rat, administration of various hormones causes an increase of blood pressure.

PRESSORECEPTORS AND HYPERTENSION. One of the interesting problems of hypertension caused by renal ischemia is the role of the pressoreceptors In the normal animal, every increase of blood pressure stimulates the aortic and carotid pressoreceptors, causing bradycardia and reflex vasodilatation. Goldblatt et al. (1940) showed that the extirpation of both carotid sinuses affects neither the development of hypertension by renal ischemia nor the level of pressure reached in the hypertensive animal. The tracings of action potentials of the carotid nerve show that in hypertensive animals, the threshold of discharge is placed at a higher level than in normal animals, showing that this has been an adaptation to the new level of pressure (McCubbin et al., 1956) However, in acute hypertension, this change of threshold seems not to occur. As the pressoreceptor reflexes start only at a higher level, not only do they not decrease blood pressure but contribute to its stabilization Some investigators believe that renal hypertension is initially produced by a humoral mechanism and that later on it is maintained by an extrarenal, probably neurogenic, mechanism

Hypertension and Pregnancy In the majority of animals with renal hypertension, pregnancy causes a decrease of blood pressure during the last period On the other hand, compression of the renal artery in the course of pregnancy exerts its usual pressor action

The decrease of pressure has been attributed to the influence of the fetal kidneys, to endocrine modifications, or to an effect of the placental circulation which is similar to that of an arteriovenous aneurysm.

Hypertension by Renal Compression. Page (1939) was able to produce persistent arterial hypertension in the dog, cat, or rabbit by wrapping the kidneys in cellophane or silk. The perirenal tissues react, forming a fibrous coat, which compresses the kidneys. This method is practical for use in small animals, in which compression of the renal arteries presents technical difficulties. Several materials, such as silk, cellophane, gauze soaked in collodium, etc., have been employed for wrapping the kidneys. Other methods include latex capsules or the compression caused by a ligature in the form of a figure eight that embraces both poles of each kidney and tends to rectify their curvature (Grollman, 1944).

In the case of unilateral perinephritis in the rat, the blood pressure rises after a latent period of 1 to 2 weeks (sometimes more). The rise is more rapid and marked and becomes permanent when both kidneys are compressed or when one kidney is removed while the other is compressed. The hypertension produced by unilateral perinephritis in the rat (in

such an irreversible change. The extirpation of the perinephritic kidney after a long period of hypertension usually is followed by a decrease of blood pressure—without complete normalization, however (Gaudino, 1944). In some of the animals, there is no drop of blood pressure; this has also been observed in the unilateral ischemia of the rabbit (Wilson and Byrom, 1941). The hypertension persisting after removal of the organ responsible for its onset may be related to the secondary arterial lesions that are found in the kidneys. The severity of the lesions found in the undamaged kidney seems to be proportional to the severity and duration of the hypertension. A truly vicious circle then occurs, so that the renal lesions cause hypertension and this contributes to the production of vascular lesions in the undamaged kidney which are capable of maintaining and increasing the hypertension. The mechanism of producing hypertension by perinephritis seems to be similar to that caused by ischemia, i.e., an ischemic effect related to the increase of intrarenal pressure without any compression of the hilus. Some authors believe that the increase of arterial pressure is caused initially by the renin-angiotensin mechanism. Later, however, it would be maintained by an extrarenal mechanism, and the removal of the kidney would not be followed by improvement.

Hypertension Caused by Reduction of Renal Tissue. Chanutin and Ferris (1932) proved that in the rat, removal of about 80 per cent of renal tissue is followed by an increase of blood pressure. Usually, from one-half to three-quarters of one kidney is resected and, in a second operation, the other kidney is removed. One to two weeks after the second operation, the blood pressure starts increasing and reaches its maximum between 2 and 4 months later. The rats show renal insufficiency, polyuria, and proteinuria. In the fragment of kidney which is left, glomerular, tubular, and vascular alterations are observed. The mechanism of this hypertension is still unknown. Some investigators believe that it could be due to renal ischemia secondary to the circulatory disturbance produced by the cicatricial retraction of the organ that has been operated upon. Even though no significant diminution of blood volume per gram of kidney is apparent, the functional overload of the fragment of kidney is such that a relative ischemia has been postulated. It is possible that this hypertension is connected to some deficiency of renal function and has a similar mechanism to that found in totally nephrectomized animals. The fact that in the rat, a reduction of renal tissue sensitizes the animal to the pressor action of several substances which are ineffective in an intact rat seems to confirm this viewpoint. These substances are Doca, sodium chloride 1 per cent, thyroid powder, tyrotropin, somatotropin, serum or placental gonadotropin (the latter in males only).

Hypertension Following Nephrectomy. Braun-Menéndez and von Euler (1947) observed an increase of blood pressure in nephrectomized rats, and Grollman et al. (1949) confirmed this observation in dogs with bilateral nephrectomy maintained alive for weeks or months through use of an artificial kidney or by means of peritoneal lavage. Without the above procedures, nephrectomy is followed by death in the dog after 3 to 7 days, a period

which is too short for producing hypertension. In the nephrectomized animal the blood pressure starts to rise between the tenth and the fourteenth days after nephrectomy. However, even before the appearance of hypertension, hemodynamic disorders occur. Forty-eight hours after nephrectomy the blood pressure is normal, but cardiac output is increased and the peripheral resistances have decreased (Krieger and Hamilton, 1958).

It is possible to cause hypertension from 24 to 48 hr after a bilateral nephrectomy by intraperitoneal administration of saline or other salt solutions (Orbison et al., 1952). In the dog, there is a direct relationship between the degree of hydration, the volume of interstitial fluid, and the hypertension. In the majority of animals the increase of blood pressure is associated with an increase in weight However, some animals develop hypertension without fluid or sodium retention. This would indicate that this is not the only factor in the production of hypertension. The increase of sodium increases the vascular lesions, the hypertension and the hyponatremia have a protective effect

Hypertension is also increased by diets rich in proteins Handler (1958) found that the administration of ACTH increases blood pressure in bilaterally nephrectomized rats Vomiting and diarrhea dehydrate these animals and prevent the increase of pressure. This hypertension seems to be due to an increase of the peripheral resistances, because no changes in cardiac output and blood volume have been found

A total sympathectomy (Houck, 1956) does not prevent the appearance of hypertension after nephrectomy, excluding the possibility of a neurogenic vasoconstriction The reactivity of the vessels to norepinephrine and other pressor substances is increased, but there is no convincing proof of the existence of pressor substances in the blood of nephrectomized hypertensive dogs. As it may be, the hypertension does not seem due to retention of pressor substances normally eliminated in the urine Moreover, bilateral ureteral ligation causes a discrete elevation of blood pressure, which reaches its maximum at about 4 days from the ligature. This hypertension seems to be connected with the circulatory disturbances caused by the hydronephrosis, and its mechanism is similar to that of the hypertension which follows renal ischemia. The blood pressure tends to drop in the following days if the life of the animal is prolonged by peritoneal lavage (Grollman et al., 1951). The unilateral ligature of the ureter also causes a transitory increase of blood pressure. If a ureter is connected to the vena cava and the other kidney is removed, retention of metabolites, as in bilateral nephrectomy, occurs. However, hypertension does not arise when the life is prolonged by peritoneal dialysis. Removal of normal renal tissue seems necessary for its production; for this reason it is thought that the renal tissue produces some hypotensive substance, the lack of which causes hypertension. The protective action of the nonischemic kidney in the form of hypertension caused by renal ischemia suggests a similar mechanism Also the transplantation of normal kidneys decreases the blood pressure in the nephrectomized dog, while other tissues do not exert this effect (Kolff and Page, 1954). It has been theorized that the normal kidney can destroy some pressor substance which forms in the organism.

In this form of hypertension, the changes of water and salt metabolism are severe and represent a factor in the production and aggravation of hypertension which will be discussed later. Increase of sodium and decrease of potassium have been found in the aortic walls of these animals It is possible that modifications of the sodium and potassium of the arteriolar musculature increase their tone and play a role in the production of this type of hypertension In chronic hypertension caused by unilateral renal ischemia of the rabbit (Daniel et al., 1954) or by unilateral perinephritis in the dog (Kolff and Page, 1955), removal of the kidney does not cause a drop of blood pressure, so that hypertension persists till death These facts can be interpreted by supposing that the chronic hypertension caused by a renal mechanism is later maintained by an extrarenal factor, or that when the kidney is removed, renal hypertension is immediately followed by the type of renoprival hypertension

The form of hypertension caused by nephrectomy has vascular alterations similar to those found in human or experimental malignant hypertension The more acute lesions represented by necrosis and hemorrhages in the heart and necrosis in the media of the small arteries and arterioles make their appearance

in the first days after nephrectomy. If the life of the animal is prolonged, hyalinization of the media is found in the arteries and arterioles The vascular lumen is usually narrowed and lateralized. Hyperplasia of the muscular tissue, subendothelial deposits of a hyaline material, and proliferation of the intima can also be found The chronic vascular lesions do not occur in the animals with ureteral ligation when life is prolonged by dialysis This led some investigators to postulate that the presence of renal tissue is able to prevent such lesions.

Other Types of Renal Hypertension. Other procedures that have been employed for the production of renal hypertension are listed on page 12-61(Supp.). Some of them are only of historical interest and will not be considered. Others, however, are interesting because they reveal mechanisms by which renal function can be altered and hypertension caused.

Kubicek et al. (1953) were able to produce hypertension in the dog by means of prolonged electrical stimulation of either the splanchnics or of the renal nerves When the stimulation is terminated, the blood pressure returns to normal These results seem to indicate that vasoconstriction can produce a renal ischemia that is sufficiently severe and prolonged for activating the renal pressor mechanism. That this activation is directly originated through a neurogenic mechanism, not through ischemia, cannot be disregarded

The changes in renal function that cause arterial hypertension may be caused by metabolic alterations. In rats, a short period of deprivation of choline or potassium during lactation is followed by hemorrhagic renal lesions and then by hypertension (Handler et al, 1951).

Masugi's experiments (1934) showed the importance of the mechanism of immunity. The renal alterations that elicit hypertension are caused by a nephrotoxic serum obtained by inoculating one animal species with the renal extract of another.

Mechanism of Renal Arterial Hypertension. With the exception of renal ischemia, the mechanism by which hypertension occurs in the various alterations of the renal function has not been sufficiently studied. It appears that in hypertension caused by renal ischemia, the increase of blood pressure is due to one or more substances poured by the kidney into the circulation. Unilateral ischemia in the dog causes a temporary hypertension, and the removal of the ischemic kidney rapidly normalizes the blood pressure. Similar results have been obtained in clinical cases with hypertension secondary to unilateral renal lesion. It is apparent that in these cases, the increase in blood pressure cannot be due to lack of production by the kidney of any hypothetic substance, neither can it be attributed to the pressor effects of renal insufficiency nor to the lack of an endocrine function of this organ. In the opinion of the author, the proofs that the hypertension caused by renal ischemia is due to renin-angiotensin mechanism seem reasonably good without being conclusive. Final proof will require greater information about the angiotensin content of the blood, in both the clinical and the experimental forms of hypertension On the other hand, the hypertension caused by nephrectomy cannot be explained by a similar mechanism. Here the hypertension is due to the lack of renal tissue, to the absence of some function of the kidney; the latter may consist in the destruction of pressor substance, the lack of a hypothetic depressor substance, or the alterations of the blood composition produced by the abolition of the excretory function. The last mechanism seems excluded by experiments in which abolition of the excretory function of the kidney without its removal is not followed by hypertension. Moreover, the healthy renal tissue protects against the pressor effect of the ischemic kidney, and bilateral nephrectomy sensitizes the vessels to the pressor action of certain substances, mainly renin The cause of the protection or potentiation is not known, it could be due to modification in the sodium and potassium content of the arteriolar muscles

The above may be summarized as follows, the hypertension caused by renal ischemia and that caused by nephrectomy cannot be explained by the same mechanism—there are at least two mechanisms by which the kidney is able to cause hypertension. It is possible that both mechanisms operate in certain cases of hypertension of renal etiology and that the increase of blood pressure depends upon the relationship between the amount of ischemic and normal renal tissues.

The Role of the Adrenal Glands in Arterial Hypertension. The role of the adrenal glands in arterial hypertension is not completely clear, even though there is no doubt that these

which is too short for producing hypertension. In the nephrectomized animal the blood pressure starts to rise between the tenth and the fourteenth days after nephrectomy. However, even before the appearance of hypertension, hemodynamic disorders occur. Forty-eight hours after nephrectomy the blood pressure is normal, but cardiac output is increased and the peripheral resistances have decreased (Krieger and Hamilton, 1958).

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1952). It is necessary to recognize that these arguments are indirect and not conclusive. On the other hand, some facts are against the participation of the kidney in this type of hypertension. Blood pressure continues to rise in rats rendered hypertensive by Doca even after bilateral nephrectomy (Hall and Hall, 1949); a kidney from such rats grafted onto a normal recipient fails to exert any pressor effect, while that of an animal with renal hypertension is capable of elevating the blood pressure (Prado and Valle, 1952). The mechanism of hypertension that persists after the administration of Doca has been studied by Green et al. (1952). The elevation does not seem to be mediated by the adrenals, thyroid, parathyroid, or gonads, however, the hypertension is reduced by removal of the pituitary and kidney

The sensitivity of animals with corticoid or metacorticoid hypertension to various pressor substances, especially renin, seems to be slightly increased. However, the interpretation of these investigations is difficult. It has been shown in the rabbit that Doca increases in vitro the sensitivity of the aortic musculature to epinephrine. There is a close relationship between Doca and the metabolism of water and sodium. Changes of the latter could be responsible for the hypertension. Doca increases the specific appetite of the rat for salt (Braun-Menéndez and Brandt, 1952) and is followed by salt retention, increase of the interstitial fluid, increase of intracellular sodium, and decrease of intracellular potassium

Pressor Action of Cortisone. Cortisone, hydrocortisone, and their derivatives may cause hypertension, either clinically or experimentally, under favorable circumstances The effect of cortisone is different from that of Doca in that it does not require the presence of sodium or potassium in order to exert its pressor effect. In the rat which is rendered hypertensive through reduction of renal tissue, the lack of potassium causes a drop in blood pressure, which can be abolished by the administration of cortisone or ACTH. Cortisone causes hypertension in adrenalectomized rats placed on a salt-poor diet; Doca has no pressor action in such animals If salt is added, then Doca causes an increase of blood pressure while the pressor effect of cortisone seems to be weaker. Actually, the pressor effect of cortisone seems to be potentiated by alterations of kidney function, loss of potassium, and adrenalectomy, but not by the lack of sodium Some fluorine derivatives, such as 9-α-fluorocortisone and 1-dehydro-9α-fluorocortisone, are several times more potent in respect to pressor action than cortisone or hydrocortisone. Paradoxically, in the majority of the cases, cortisone is able to abolish the hypertension that develops in parabiotic rats.

Corticosterone in doses of 5 mg per rat, per day, causes hypertension, polydypsia, and vascular lesions (Skelton, 1958).

Aldosterone. Primary hyperaldosteronism is accompanied by hypertension; in hypertension, aldosterone excretion seems to be increased. In the rat, a dose of from 0.25 to 1 μg of aldosterone per day causes arterial hypertension and vascular lesions (Kumar et al., 1957). However, other investigators proved that aldosterone administration in the rat has little or no pressor effect (Fregly and Arean, 1959), thus establishing a clear difference between the actions of Doca and aldosterone. No doubt further studies are needed in this field.

Hypertension Caused by Regeneration of the Adrenal Glands. The regeneration of the adrenal cortex in young female rats which have undergone unilateral nephrectomy and which drink a 1 per cent sodium chloride solution causes hypertension and vascular lesions similar to those produced by several corticosteroids or their derivatives (Skelton, 1956). The administration of saline solution is essential for the onset of hypertension, but when hypertension has been established, saline solution can be omitted without causing a decrease in blood pressure. Ligation of the adrenal pedicle causes a similar picture Adrenal-enucleated rats present periarteritis nodosa, panarteritis, fibrinoid degeneration, and arteriolar wall necrosis, these lesions are similar to those found in malignant renal hypertension and in corticoid or metacorticoid hypertension.

MECHANISM OF ARTERIAL HYPERTENSION BY ADRENAL REGENERATION. The hypertension is clearly associated with the regeneration of the adrenal glands. If after enucleation or transplantation of the gland, its regeneration is inhibited by removal of the pituitary, the hypertension fails to appear. Substances such as anferone B which block the synthesis of corticoids by the adrenal glands also have an inhibiting effect. Somatotropin and thyroxin,



Fig. 12-10. Nephrosclerosis produced by DOCA. Two glomeruli showing different degrees of sclerosis. One arteriole shows fibrinoid degeneration of the media; the other shows replacement of the media by connective tissue. Gomori's aldehyde fuchsin. ×160. (*From Skelton A M A. Arch. Path.* 1955)

glands do play such a role. It is known that it is possible to produce hypertension through the administration of desoxycorticosterone, cortisone, corticosterone or one of its derivatives, and also through the enucleation of the adrenal glands. In renal hypertension, changes of the adrenal glands have been observed and their surgical removal decreases or normalizes blood pressure.

PRESSURE ACTION OF DESOXYCORTICOSTERONE. Desoxycorticosterone is able to produce increased arterial pressure in several species but the rat is the animal in which its effect has been best studied (Selye et al., 1943) (Fig. 12-10). The drug is administered in the form of oil or microcrystals, in a daily dose of 1 to 2 mg. It is conveniently given through subcutaneous implantation of pellets containing around 20 mg Doca. Desoxycorticosterone produces an increase of arterial pressure in normal rats, suprarenoprives, or rats with renal hypertension. The arterial pressure starts to ascend after the first week, to reach its maximum in 6 to 8 weeks.

The pressor effect of Doca is potentiated by the salt content of the diet. Moreover, in the absence of sodium, Doca fails to exert any pressor action and does not produce the typical vascular alterations. Potassium seems also to be indispensable for the development of the pressor action (Rosenman et al., 1954). A decrease of renal tissue increases the effects and makes it possible to obtain a more rapid and constant hypertension It is customary to sensitize the rats through a unilateral nephrectomy, and to replace water in the diet by a 1 per cent solution of sodium chloride. The pressor effect of Doca persists in a large percentage of animals after withdrawal of the drug; this has been called *metacorticoid hypertension*.

ANATOMIC ALTERATIONS PRODUCED BY DOCA. The administration of Doca causes vascular lesions in the heart and kidneys, but also in other organs. The kidneys become hypertrophied; microscopically they show glomerular and tubular lesions. The glomeruli show deposits of hyaline material (fibrinoid) and fibroplastic periglomerular proliferation. These alterations may evolve to a complete glomerular fibrosis. The arteries and arterioles show hyaline degeneration of the media and necrosis of the vascular walls. The media may be replaced by connective tissue, while the intima shows deposits of a subendothelial hyaline material with total or partial occlusion of the lumen of the artery. The renal tubules are distended and full of hyaline material. The vascular lesions of other tissues are similar to those of the kidneys but less severe. Methyl-androstenediol, an androgenic steroid, can cause hypertension with lesions similar to those described above (Skelton, 1955). Selye (1944) observed that this sclerotizing action of Doca and of other related substances is neutralized by other steroids, derived from the androstane, which produce tubular hypertrophy and hyperplasia without sclerosis

MECHANISM OF THE HYPERTENSION CAUSED BY DOCA. The mechanism of hypertension caused by Doca is obscure. The predominance of renal vascular lesions leads one to suspect the participation of the kidney. Several facts seem to confirm this viewpoint: (1) the hypertension is potentiated by partial nephrectomy, (2) total nephrectomy decreases the metacorticoid hypertension (Green et al, 1952), even though it seems ineffective *during* Doca administration, (3) the pressor effect of renin is less marked in adrenalectomized animals and is greater in animals treated with Doca and salt; Doca decreases the renin content of the kidneys, (4) administration of renin increases the vascular alterations produced by Doca, injected in rats rendered hypertensive by means of Doca and salt, it causes a picture similar to that of eclampsia, with convulsions, edema, oliguria, azotemia, anasarca, and tubular necrosis (Masson et al,

an important role in hypertension. Its removal does not affect the blood pressure of animals with renal hypertension, but injection of pitressin is followed by a drop of blood pressure in the rat with renal hypertension or hypertension caused by administration of Doca (Friedman et al, 1955). This action of pitressin seems to be related to modifications in the excretion of electrolytes The urine of hypertensive subjects (man, dog, rat) has demonstrated a greater antidiuretic activity than the normal urine It is possible that this fact is related to the alterations of water and salt metabolism that are commonly found in hypertension

In conclusion, a deficiency of pituitary function tends to decrease the hypertension, while an excess has an opposite effect. The mechanism of this action is not completely clear, but most data seem to indicate that it is closely linked to the adrenal function. An adrenal deficiency resulting from hypophysectomy is probably responsible for the fall of blood pressure in the hypertensive subject The hypertensive action of the anterior lobe of the pituitary gland and of somatotropin is likely to be obtained through a stimulation of the adrenal glands

The Thyroid. Thyroidectomy has no effect on blood pressure in the dog with hypertension caused by renal ischemia However, in the rat with renal hypertension, thyroidectomy or the administration of propylthiouracil reduces the level of blood pressure or prevents hypertension These measures also reduce the blood pressure of the rat treated with Doca and salt, and prevent the increase of blood pressure and the vascular lesions occurring in this condition Thyroidectomy also protects against nephrosclerosis and myocarditis in the form of hypertension caused by methyl-androstenadiol and chlorocortisol Thyroid administration elicits an increase of blood pressure in the partially nephrectomized rat. Thyrotropin has a similar action in animals with intact thyroid but not in thyroidectomized animals (Braun-Menéndez and Penhos, 1953)

The mechanism of the thyroid pressor effect is unknown. It has been shown that the reactivity of the vessels to pressor substances is increased in animals treated with thyroid extract, and is decreased after thyroidectomy.

Other Glands. The parathyroids, the gonads, and the pancreas do not seem to be connected with the mechanism of production of hypertension The removal of the medulla of both adrenal glands does not modify the blood pressure of animals with renal hypertension. The gonadotropins of the serum or corion have a pressor action in the male partially nephrectomized rat.

Sodium and Potassium in Arterial Hypertension. The modifications of the water and salt sodium balance in hypertension have been intensively studied, and their importance has been recognized in the last 10 years However, some of the typical changes that follow hypertension seem to be related more to the simultaneous renal changes than to the pressor mechanism

MODIFICATIONS OF THE HYDROSALINE METABOLISM IN HYPERTENSIVES. The rat with renal hypertension produced either by reduction of the renal mass or by compression of the kidney (ligature-in-eight or perinephritis) shows marked alterations of water and salt metabolism. Polyuria, polydipsia, and reduction in the concentration power of the kidney are produced The interstitial fluid increases, mostly in the initial stages of hypertension, but blood pressure may rise without such an increase. If the hypertensive rat can choose between drinking water and a sodium chloride solution, it prefers the latter whenever the molarity of the solution is less than 0 06 *M* (Fregly, 1959); if the molarity is above 0.075 *M*, it prefers water. Normal rats with a similar alternative choose the salt solution until a concentration of 0.105 *M* is reached, i e , they accept solutions having a greater molarity. The rat rendered hypertensive through Doca or cortisone administration or by adrenalectomy shows alteration of water and salt sodium balance similar to that described above.

The velocity with which the kidney eliminates an overload of sodium is increased in human hypertension, as well as in experimental renal or adrenal hypertension The above alterations of water and salt metabolism are not limited to the hypertensive animal but are also found (though to a less marked degree) in animals which have been submitted to the same experimental procedure but which have not developed hypertension It seems reasonable to assume that they are due to some degree of renal insufficiency. This seems confirmed by the fact that in the dog, where renal ischemia is followed by hypertension

however, potentiate this hypertension; ACTH fails to exert any significant action. Removal of the thyroid gland prevents the occurrence of hypertension. It has been thought that hypertension and the vascular lesions are the result of an increase in secretion of the regenerated gland or of a hormonal imbalance However, no increase of aldosterone or corticosterone was found in the blood of the renal vein on the side of the regenerated gland (Brogi and Pellegrino, 1958; Masson et al, 1958). Actually, the aldosterone content seems to be diminished.

The magnitude of the renal lesions has concentrated attention on the kidneys as the organ responsible for the hypertension, but, so far, there are no conclusive data

The Adrenal Glands in Renal Hypertension. In hypertension caused by renal ischemia in the dog, all the investigators have found that the removal of the adrenal glands causes a fall in blood pressure to normal or subnormal levels Renal ischemia in the adrenalectomized animal is not followed by hypertension. The administration of cortical extract restores the hypertension, but the level of blood pressure existing prior to adrenal removal is not reached.

In the rat rendered hypertensive by perinephritis, adrenalectomy is followed by a drop of blood pressure to normal or subnormal levels, and the arterial pressure can be increased again by administration of Doca. On the other hand, it has been found that it is possible to obtain hypertension in the adrenalectomized rat through wrapping the kidneys in a latex capsule. In the hypertension caused by nephrectomy, subsequent adrenalectomy fails to produce a fall of blood pressure, even though there are some discordant results In regard to the adrenal changes in renal hypertension, hypertrophy of these glands has been found in rats made hypertensive by perinephritis

Substances That Block Corticoid Action. Sturtevant et al. (1959) studied the effect of one steroid (SC 5233) in adrenalectomized rats receiving Doca and found that it is able to reverse the trend toward sodium retention and loss of potassium. It also blocks the urinary effects of aldosterone, hydrocortisone, and other steroids It has no androgenic, anabolic, or estrogenic effects SC 5233 inhibits the development of hypertension by Doca and reduces the metacorticoid hypertension in the rat. Another steroid (SC 6584) has similar characteristics in the metacorticoid and perinephritic hypertension of the rat, thus revealing the role of the adrenal glands in renal hypertension.

Role of the Pituitary Gland. Because of contradictory experimental results, the role of the pituitary in renal hypertension is not clear. *Total extracts* or *somatotropin* increase blood pressure in the rat (Selye, 1951). Somatotropin is the most effective, mostly in rats with unilateral nephrectomy, though it seems to be ineffective in thyroidectomized rats Somatotropin causes an increase of weight of the abdominal organs, produces nephrosclerotic lesions, and aggravates the renal lesions produced in rats by choline deficiency as well as the vascular lesions produced by methylandrostenediol (Selye and Salgado, 1957). Selye and Bois (1956) found that the nephrotoxic effect of somatotropin in the rat is potentiated by ACTH, and that the adrenal glands are necessary in order for it to occur. It is possible that somatotropin acts by liberating or increasing the production of some steroid or that it needs the presence of some hormone normally produced by the adrenal glands in order to exert its action. *ACTH* seems to have shown also its pressor action in special conditions (Handler and Bernheim, 1950), and is able to produce important vascular lesions in the adult rat with unilateral nephrectomy (Wexler and Miller, 1958).

Removal of the pituitary gland causes a drop of blood pressure in the dog, as well as in the rat, with renal hypertension. In the dog, the blood pressure can reach either normal levels or a slightly higher level In the hypertensive rat, hypertension can be restored by ACTH administration In dogs in which the pituitary gland has been removed, renal ischemia causes an increase of blood pressure, and, if there is a subsequent drop, increase of the ischemia is followed by a new increase of blood pressure

Hypophysectomy also reduces the endocrine form of hypertension. Removal of the pituitary gland is followed by a drop of blood pressure and a decrease of the vascular lesions in rats that have been treated with Doca (Hall and Hall, 1959)

POSTERIOR LOBE OF THE PITUITARY GLAND. The posterior lobe does not seem to have

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without alteration of the excretory function of the kidneys, the alterations of water and salt metabolism are not clearly present.

THE SODIUM AND POTASSIUM OF THE TISSUES The electrolyte composition of the tissues has been intensively studied, but the results are difficult to interpret. On the one hand, the intracellular fluid composition varies in various tissues of the body and it would be incorrect to extend to all tissues the data obtained in one. On the other hand, the composition of the intracellular fluid is deduced on the basis of data obtained from analysis of a fragment of tissue, so that it is necessary to advance certain hypotheses which are not totally justified. The results of Tobian and Binion (1954) showed that the content of sodium and potassium is increased in the aorta of rats which have renal hypertension or which have received Doca. The hypertensive action of certain drugs, such as reserpine, is associated with the decrease of these cations in the aorta, and potassium restriction has a similar effect. In rats made hypertensive by renal compression, restriction of potassium in the diet is followed by a drop of blood pressure and a decrease of potassium in the aorta, an effect that can be reversed by the administration of cortisone. Potassium restriction also reduces the blood pressure of normal rats, again together with a decrease of potassium in the aorta. The blood pressure can be normalized by the administration of cortisone.

THE SODIUM AND POTASSIUM OF THE DIET The pressor effects of an overload of sodium have been studied in several conditions, and the results are generally similar. In the rat, the administration of a diet rich in sodium causes hypertension which is associated with renal insufficiency and vascular alterations (Meneely et al, 1953). In birds, Selye has described a sclerotizing effect on the kidney resulting from the administration of an excess of salt. In the nephrectomized dog, ingestion of saline solutions accelerates the appearance of hypertension, and partially nephrectomized rats become hypertensive if they drink a 1 per cent salt solution One per cent or 2 per cent potassium solutions have no pressor effect in partially nephrectomized rats Sodium restriction somewhat reduces renal hypertension and counteracts the hypertensive action of Doca but not that of cortisone. Restriction of potassium causes a reduction of the effect of Doca but not of cortisone. Potassium deficiency, prolonged for some weeks, causes in the rat renal alterations (glomerular atrophy and tubular dilatation) which are able to cause hypertension.

MECHANISM OF THE VASCULAR ACTIONS OF SODIUM AND POTASSIUM. The above-mentioned facts show that modifications in water and sodium balance somehow are involved in the mechanism of hypertension. It is not clear, as yet, how these alterations succeed in causing vascular effects, but some of the possibilities should be discussed.

Change in Vascular Sensitivity. The resting potential of several excitable tissues (nerve, smooth, and skeletal muscles) depends upon the relationship between the electrolyte concentrations (especially potassium) within and outside the cell. Bohr et al. (1958), working with fragments of rabbit aorta in Krebs solution, observed that the response to epinephrine increases when the sodium concentration in the fluid decreases, and vice versa On the contrary, if the potassium concentration was increased, the sensitivity of the preparation increased, and if it was reduced, it decreased. Similar results have been obtained in sections of colon (Friedman, 1959). The pressor effect of several drugs seems to be associated with a shift of sodium from the intracellular to the extracellular fluid. Although the electrolyte changes in the arteriolar muscle in hypertension are not known, these studies favor the concept that modifications in the reactivity of the vessels to vasoconstrictor substances play a certain role in the pressor effects of sodium and potassium

Renal Alterations. The vascular and renal alterations produced by an overload of sodium or a potassium deficiency seem to point out that the hypertension obtained in such way may be produced by a renal mechanism. At present, however, there is not enough evidence to confirm or deny such a possibility.

Alterations of the Adrenal Function. The aldosterone secretion is controlled by the extracellular concentration of sodium and potassium and also by the volume of the liquid compartments Increase of potassium, diminution of sodium, and reduction of the extracellular volume increase the production of aldosterone It is possible to postulate that if the secretion of aldosterone is excessive, an endocrine imbalance would occur, causing renal

and vascular alterations, followed by hypertension

Arteriolar Edema The increase of water in the arteriolar wall could reduce the vascular lumen and increases the total peripheral resistance, thus favoring hypertension.

NEUROGENIC ARTERIAL HYPERTENSION

Increase of Intracranial Pressure. It is well known that a sudden increase in the pressure of the spinal fluid causes arterial hypertension. Dixon and Heller (1932) showed that it is possible to obtain persistent hypertension in the dog through cisternal injection of a suspension of kaolin. This substance causes an obstruction of the subarachnoid spaces, limiting the reabsorption of fluid and causing an increase in intracranial pressure. Not all investigators are in agreement about the possibility of obtaining permanent or persistent hypertension with this procedure. Some have shown that the increase of blood pressure is moderate or transitory. The arterial hypertension caused by intracranial hypertension seems to be due to *anoxia of the vasomotor centers*, secondary to the ischemia that results from the compression of the central nervous system The sympathetic stimuli discharged by the vasoconstrictor center cause a reduction of the arteriolar lumen and probably a discharge of epinephrine or norepinephrine by the adrenal medulla According to some investigators, renal denervation prevents or cures this form of hypertension, this would suggest that the renal pressor system can be activated by sympathetic hypertonus.

Section of Carotid and Aortic Nerves. Koch and Mies (1929) obtained a persistent hypertension in the rabbit through section of the aortic and carotid nerves Other investigators confirmed these results in the dog (See Fig 12-11) The blood pressure remains elevated for years, but in some animals shows a tendency to drop and may become normal, a fact which has been attributed to regeneration of the vasodepressor trunks The increase in pressure obtained with this method is considerable, the systolic pressure may even reach 300 mm Hg The blood pressure increases abruptly after section of the last depressor nerve, but this increase is of short duration Usually, persistent hypertension starts 48 hr after cutting of the nerves and reaches its maximum value

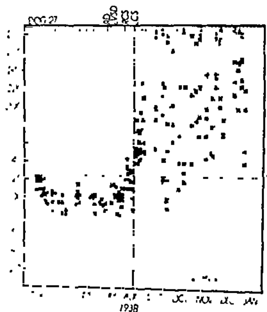


Fig. 12-11. Effect of the resection of the depressor nerves Diastolic pressure in millimeters of mercury. *RD*, resection of the right depressor nerve; *LVSD*, section of the left vagosympathetic trunk; *RCS*, section of the right carotid sinus, *LCS*, section of the left carotid sinus (*From Bedell Thomas, Bull Johns* Hopkins Hosp. 1944.)

between the second and fourth weeks The hypertension is accompanied by an increase of cardiac rate, the tachycardia usually being proportional to the elevation of pressure. Both the cardiac rate and the blood pressure present large fluctuations. Rest or sleep causes decrease of both, and may even produce normal levels On the other hand excitement or exertion increases considerably both the blood pressure and the cardiac rate. It is interesting to note these characteristics, which are different from those of renal hypertension, in which the pressure level is practically stable. Thoracic sympathectomy, including the stellate ganglia, normalizes the pulse rate but causes only a slight decrease in blood pressure This shows, on the one hand, that hypertension is not caused by the tachycardia and, on the other, that the tachycardia is mainly due to unopposed tonus of the cardioaccelerator center. Total sympathectomy prevents or abolishes almost completely the hypertension caused by section of the carotid and aortic nerves (Heymans and Bouckaert, 1935) Consequently, this type of hypertension seems to be due to an increase of sympathetic

tonus, secondary to the section of the depressor nerves. It is known that the tonus of the vasomotor center is inhibited by stimuli carried by the depressor nerves. When these stimuli are abolished, a hypertonus of the sympathetic center occurs, with subsequent hypertension and tachycardia.

The sudden and transitory increase of blood pressure which occurs immediately after the resection of the depressor nerves seems to be due, in part at least, to an increase of cardiac output, possibly resulting from a discharge of epinephrine by the adrenal medulla.

In the stage of chronic hypertension, some investigators have found vasoconstrictive activity in the blood, but this activity has been denied by others. The participation of epinephrine or norepinephrine has been assumed on account of the marked depressor effect which sympatholytic drugs exert in this condition. One of the most interesting phenomena is the latent period that exists between the section of the depressors and the onset of permanent hypertension. This has been attributed to an initial and transitory heart failure which is caused by the tachycardia and which would decrease cardiac output. Another theory explains this latent period as the necessary interval for the activation of some other pressor mechanism, according to this view the kidney contributes to the maintenance of the high level of pressure. The renal pressor mechanism could be activated by renal ischemia resulting from diffuse vasoconstriction or could be caused directly by impulses coming along the renal nerves. It has actually been shown that stimulation of the nerves of the renal pedicle can produce hypertension. Even though renal denervation does not cause a marked drop of blood pressure in these animals, the experiments of Grimson, Bouckaert, and Heymans (1939) have shown that the kidney plays a definite role in this type of hypertension. They found that if the entire sympathetic chain, except the renal innervation, is removed, there is a decrease of blood pressure but normal values are not reached. A subsequent resection of the renal nerves, on the other hand, completely normalizes the blood pressure. It seems that the hypertension is caused by sympathetic hypertonus directly acting on the vascular system and indirectly activating the renal pressor system.

Cerebral Ischemia. Nowak and Walker (1930) demonstrated that a ligature of the carotids, vertebrals, and spinal arteries made by subsequent steps in order to permit the establishment of collateral circulation, is followed by persistent hypertension in the dog. This has been subsequently confirmed in other species. The mechanism of this type of hypertension has not been much studied, but it seems reasonable to suppose that the hypertension, like that produced by cerebral compression, is caused by the effects of ischemia of the vasomotor center. This is stimulated and, by sending sympathetic impulses, causes diffuse vasoconstriction and increase of peripheral resistance. Bilateral compression of the carotid sinus area, including the external and internal carotids, produces persistent hypertension in the dog. Bilateral compression of the carotids *above* the sinus also causes hypertension (Wakerlin et al., 1954), giving the impression that the effect of carotid sinus compression may be attributed to cerebral ischemia. This hypertension is not associated with tachycardia.

10

The surgical correction of hypertension of renal vascular origin

JAMES A. HUNTER AND ORMAND C. JULIAN

The problem of arterial hypertension has been much investigated, with particular emphasis on the role of the kidney in its pathogenesis As long ago as 1836, Bright related hypertension to disease of the kidney Renal-related humoral mechanisms, renin and VEM (vasoexciter material), have been extensively studied in the laboratory, and their roles postulated Endocrine factors, particularly adrenal and thyroid gland relationships to hypertension, have been pursued. Goldblatt's demonstration (1934) that experimentally induced renal ischemia produces hypertension remains a most important contribution and, indeed, one of the best-known experimental works

Clinical observation and investigation have established a substantial list of pathologic states associated with hypertension, many of them related to renal disease. However, many patients with hypertension defy specific etiologic diagnosis and are considered to have "essential" or, perhaps better, "idiopathic" hypertension Despite important strides in the symptomatic medical treatment of elevated blood pressure, without regard to its cause, such management has numerous limitations and is not characterized by cure. On the contrary, hypertensive patients are cured, and the serious cardiac, renal, cerebral, vascular, and ocular sequelae arrested or prevented when a specific etiologic diagnosis can be made and corrective surgical measures applied.

The clinical importance of hypertensive disease of renovascular origin relates to the fact that in patients with blood pressure elevation due to such a cause, a specific diagnosis can be made and often a surgical cure effected.

Prior to the current decade, with its renewed interest in renovascular hypertension, there was an era of distinct disappointment and even skepticism regarding operative procedures for hypertension During this period, *nephrectomy* was applied for unilateral disease of the kidney, and the cure rates were not impressive, failing to exceed 26 per cent (Smith, 1948, 1952, Smithwick and Thomson). Improved understanding of the pathophysiology of renal hypertension, the availability of better diagnostic techniques, and the development of cardiovascular surgery with its technical skills, all have served to renew interest in this field and vastly to improve results

Lesions affecting the renal vessels that may result in secondary systemic hypertension include renal artery stenosis, renal arteriovenous fistula, renal artery occlusion, and aneurysm of the renal artery Hypertension results in the presence of such lesions because of the altered renal arterial flow or diminished arterial pulse pressure The importance of pulse pressure alterations in the production of renal hypertension has been demonstrated both clinically and experimentally (Morris et al, 1960a, Hawthorne et [illegible]

of [illegible]

zy[illegible]

pa[illegible] reactions involving a hepatic protein substrate and resulting in the formation

of a potent vasopressor substance (*angiotensin*).[1] The object of therapy is to restore, where possible, normal renal hemodynamics and relieve the hypertension.

RENAL ARTERY STENOSIS

After Goldblatt's original publication (1934), there appeared sporadic reports of hypertension due to renal artery stenosis. It remained, however, for the publication of Poutasse and Dustan (1957) to rekindle interest in this entity. More recently, numerous publications have been devoted to the subject and the total number of cases reported has rapidly increased.

Although by far the principal single cause of arterial stenosis is *focal arteriosclerotic disease*, there are multiple, less common causes The lesion may be congenital or acquired, with the former resulting in symptomatic hypertension during early childhood The varieties of nonarteriosclerotic stenosis include simple idiopathic congenital stenosis, stenosis due to fibromuscular hyperplasia (Wylie and Wellington), arteritis involving the renal arteries (Danaraj and Wong), syphilitic occlusion of the renal vessels (Price and Skelton), compression and stenosis of the arteries by malignant neoplasm (Blatt and Page), narrowing of a renal artery by a fibrous band (Imber and Clymer), distortion and narrowing of an artery by a hydatid cyst (Davson), compression of a renal artery by an aortic aneurysm (Hoffman), stenosis of the arterial orifice by a dissecting aneurysm (Case report M. G. H.), and renal arterial narrowing associated with coarctation of the abdominal aorta (Brust et al.)

The incidence of hypertension due to renal artery narrowing will relate to the index of suspicion of the physician. No age group is exempt, the diagnosis having been made in infants (De Camp and Birchall), as well as in adults in their eighth decade of life

The clinician's suspicions should be particularly aroused when the following clues are encountered. (1) significant hypertension in children or young adults in whom no other cause of secondary hypertension can be demonstrated; (2) hypertension of abrupt onset, (3) elevated blood pressure in patients with a history suggestive of renovascular accident; (4) severe hypertension that rapidly progresses to the malignant phase; (5) mild hypertension that suddenly becomes severe; (6) malignant hypertension in the older age group; (7) hypertension in a patient with known arteriosclerotic disease elsewhere in his vascular tree

Physical findings in patients with renal artery stenosis are seldom diagnostic. Although nonspecific, the cardiac and ocular sequelae of the pathologic blood pressure may be apparent and will reflect the physiologic importance of the hypertension. As is proper in all hypertensive patients, signs of coarctation of the aorta should be sought and proved absent. A careful bedside examination of the peripheral arterial system should be made to detect the smallest finding indicative of arteriosclerotic change. For example, a patient who has marked hypertension and one who has *a systolic bruit over an iliac artery* indicating the presence of arteriosclerotic disease may have similar involvement at the orifice of a renal artery. *Bruits over the renal area* have been uncommon in the authors' experience; when noted anteriorly, they are more often due to associated change in the aorta or iliac vessels. Careful auscultation should always be performed, both anteriorly and posteriorly, but one should realize that absence of the systolic bruit in no way excludes the diagnosis.

Routine investigations of the urinary tract are usually negative. Initial studies of the patient will include urinalysis, blood urea nitrogen or nonprotein nitrogen determination, chest x-ray, and electrocardiogram. Study of the urine will help to rule out renal parenchymal diseases such as nephritis that may result in hypertension Except in an infrequent patient with major bilateral narrowing of the renal arteries, there will be no azotemia. The electrocardiogram and roentgenogram will permit further definition of the cardiac sequelae of the hypertension.

The *intravenous pyelogram* deserves special mention

The technique of pyelography is altered in patients with hypertension, first films being obtained at 30 sec and 2 min, in addition to the customary 5-min study. An attempt is thus made to record the *nephrogram* and early appearance of the dye, so that bilateral function may be compared. Although it does not invariably do so, the kidney with arterial involvement may show a phase of delayed excretion on these early films Such a finding

[1] See Part 2, Chap. 27, for "physiology of renal circulation," and Chap 5, this Part, for the "humoral mechanism of hypertension" *Editor*

is of major importance, and is strong indication to proceed with studies as outlined below. A comparison of renal size is made from the x-rays Occasionally the involved kidney will be demonstrably *smaller* than its partner. Perhaps the most important comment to make in relation to the pyelogram is that in the classical instance of renovascular disease, this examination is normal Indeed, the greatest opportunities for cure lie in those patients who have essentially normal studies (Squire and Schlegel).

Specialized studies are then performed as indicated, to evaluate the hypertension further. These include the *radioisotope renogram*, differential studies of renal excretion, and *aortography* The use of ganglion-blocking agents, such as tetraethylammonium chloride, in diagnosis has not been helpful. The latter examination, when positive, is said to result in either a pressor response or in no fall in blood pressure (Brust and Ferris).

The simplest of the specialized examinations, the radioisotope renogram, is an excellent screening test to detect alterations in renal blood flow. The test is readily performed, the amount of irradiation received is minimal, and the cost is low.

Principally, the study involves the intravenous injection of a *radioisotope-tagged substance*, such as *Diodrast* or *Hippuran*, and then the recording of appearance and intensity at the renal areas. The gamma irradiation can be counted and charted in relation to time, and the two sides compared The initial peak of appearance relates directly to renal blood flow and, therefore, has particular importance

Most valuable in comparing the sides, when the normal kidney serves as a control, the results may be more difficult to evaluate when there is bilateral stenosis, and thus a symmetrically altered result. It is anticipated that this examination will come to be the main study utilized to screen candidates for aortography.

Work in the experimental laboratory by Mueller et al, H L White, and others has demonstrated that in renal ischemia, electrolyte excretion by the kidney is decreased In particular, *less sodium is excreted*, and the total volume output of that kidney is also diminished This principle, popularized by Howard et al (1954, 1956), is applied clinically in the use of split function studies when renal artery lesions are suspected The ureters are intubated, and urine collections are made in chemically clean glassware. Differential function studies, phenol sulphonphthalein excretions, and more complex clearance studies can then be performed as desired As with the radioisotope renogram, the most impressive results are obtained in patients with unilateral disease, when there is opportunity to contrast the sides. Reduction of volume excretion by 50 per cent and of sodium excretion by 15 per cent or more indicates a positive test (Connor et al). Shortcomings of this study include the necessity of *ureteral catheterization*, with the essential instrumentation and the possibility of inducing infection, technical difficulty relating to traumatic hematuria, leakage of urine about the collecting catheters, and the fact that results may not be definitive in bilateral disease, or even in unilateral disease. The data so obtained may be especially helpful in assisting in evaluation when aortography has led to the suspicion of a renal artery lesion

An operative prerequisite, and a necessary final examination before diagnosis can be conclusively established, is *aortography*. All the other studies, by virtue of their positive or negative results, reflect on the probability of there being a renovascular lesion. They are not, however, able to prove or disprove the diagnosis absolutely. The aortogram permits positive diagnosis, defines the anatomy of the lesion, directs the therapy, and permits speculation as to prognosis. One may consider the "work-up" of a person suspected of having renal arterial disease as proceeding in two phases: (1) preliminary studies, and (2) aortography.

In view of the importance of the aortogram in the final demonstration of the lesion, it is well to list the types of patient for whom arteriography is indicated.

1. Hypertensive patients who, when studied as outlined above, reveal data increasing the probability of a renal arterial lesion Anyone with a positive differential excretory study or radioisotope renogram should be subjected to aortography.

2. Young patients, certainly those under the age of 35, and especially children, in whom there is significant hypertension

3 Persons with established recent onset of blood pressure elevation

4 Patients with severe hypertension rapidly progressing to the malignant stage.

5 ...

...alignant hypertension.

6 Patients with demonstrable arteriosclerotic disease, especially of the aorta and iliac channels, plus hypertensive disease

7. Hypertensive patients with a history suggestive of a renovascular accident

8 A patient whose hypertensive disease is of progressive physiologic importance and who demands maximum study and therapy to alter an unfavorable prognosis

In the experience of the authors and of others aortography has been accomplished with little risk and with excellent results in terms of the data obtained

Two techniques are used (1) the translumbar percutaneous puncture of the aorta, (2) the retrograde method through a femoral artery With few exceptions, the *translumbar approach* is used in adults. Twenty to twenty-five milliliters of 70 per cent Urokon injected high in the abdominal aorta is usually adequate to outline the renal branches Simultaneous definition of iliac, femoral, and major lower extremity channels may be desirable in adults with arterial disease altering blood flow to the legs The main application of the *retrograde method* is in children, the authors have used it in children as a method of choice This approach may also be desirable in the occasional adult who is significantly ill, usually from cardiac complications of the hypertension, and in whom it is desirable to avoid the prone position with general anesthesia Using general anesthesia in children, and local anesthesia in adults, the femoral artery is exposed through a small skin incision, a transverse arterotomy performed in the common femoral artery, and the catheter passed proximally to the upper abdominal aorta Five to eight milliliters of 50 per cent contrast material will outline the aorta and its branches in a satisfactory manner in a child Perfection in technique is essential to either rule out the lesion with confidence or permit definition adequate to direct operative repair The procedure must be conducted technically in such a way as to shield and safeguard the operating personnel In the latter regard, adequate lengths of connecting tubing are a prerequisite to allow injection from behind a lead screen Ordinarily, the interpretation of the aortogram is not difficult Most commonly the narrowing will be noted at the origin of a single large renal artery. On occasion, the lesion occurs in a more distal portion of the artery, as is often the case when the etiologic factor is *fibromuscular hyperplasia Stenosis* may less commonly be seen in one of the secondary divisions of the main vessel Generally, a single film exposure on a 14 by 17 in cassette adequately records each injection When studying an unusual lesion, it may be necessary or desirable to use x-ray equipment that will permit multiple exposures during the single injection The authors have, for example, found this technique useful in studying a small hypertensive child whose kidneys were supplied by no less than six small arteries, precise definition of all six on a single film would have been difficult Most often, poststenotic dilatation is seen distal to the point of arterial obstruction, this finding confirming the presence of a true stenosis and differentiating it from artifact or spasm One may sometimes find indirect help in interpreting a questionable finding by reviewing the results of the differential excretion and radioisotope studies

During the past decade, the management of renovascular disease has undergone important changes. As this is an era of reconstructive vascular surgery, the principle has become one of repair rather than eradication of the involved part. Nevertheless, the surgeon is left a choice, except in bilateral lesions, of removing the involved kidney or of effecting an arterial repair The indications for reconstruction or nephrectomy thus merit review. The procedure of choice is restoration of normal renal arterial flow, for the following reasons·

1 In bilateral disease this is the only method available

2 A maximum of functional renal tissue is preserved.

3 The kidney supplied by the involved artery may be the better kidney of the two.

The latter statement is based on the *excellent evidence that stenosis protects the involved kidney from the impact of the hypertension it has produced, whereas there is no such mechanism to protect the contralateral organ*. Histologic studies from the two kidneys in instances of unilateral disease have shown significant arteriolar nephrosclerosis on the side with a normal arterial anatomy, and the absence of such changes on the side of arterial narrowing One would, therefore, anticipate that restoration of a normotensive state would most consistently follow bilateral renal arterial reconstruction, as both kidneys have been protected from the tension elevation, such has been found to be the case Patients with unilateral disease may have a slower response, or even an incomplete one, in terms of blood pressure reduction because of the perpetuating tendency of the arteriolar disease on the opposite side to maintain a pressure elevation It follows that, in all likelihood, a patient will be

encountered in whom the successful restoration of normal blood pressure will only follow *reconstruction of the narrowed artery and then nephrectomy* on the opposite side Such a case, to the authors' knowledge, has yet to be reported, but this would seem to be only a matter of time.

Nephrectomy is indicated (1) in the management of the anatomically unfavorable arterial lesion, such as that presenting several areas of stenosis in the patient with multiple small renal arteries, (2) in the treatment of the very ill patient with unilateral disease who is a grave surgical risk Fortunately, these two circumstances are infrequently encountered It is true that extraperitoneal nephrectomy is a simpler and more rapid procedure

A variety of methods and techniques of arterial reconstruction have been reported These include *endarterectomy* of the involved segment, *bypass graft* between aorta and renal artery distal to the stenosis, *longitudinal sectioning of the stenotic artery* and then *application of an onlay patch graft* to enlarge the circumference, *division of the artery with adjacent reimplantation*, and *splenorenal arterial anastomosis*

length by carrying the dissection outward from their aortic origin If exposure of the distal divisions of the artery is desired, improved access may be gained with extraperitoneal dissection, beginning at the paracolic gutter laterally. Although exposure of the origin of the renal artery and its proximal main trunk is the easiest method, by combining these two medial and lateral approaches, any portion of the extranephric vessel may be achieved As most of the stenoses occur at the proximal end of the renal artery, exposure in the average case is not hard to achieve The narrowed segment is then examined and the distal, generally dilated, segment is palpated to elicit the presence of a thrill or diminished pressure. It is desirable at this point to determine pressures proximal and distal to the obstruction and to establish *the gradient* that it has produced. The character of the proximal renal artery or aorta, and also of the distal vessel, is then evaluated and the method of surgical repair decided upon. In children, one is very much more restricted in the selection of a method of reconstruction because of the necessity of avoiding the use of prosthetic materials. This is especially so in very small children who have a major growth potential Wherever possible in the pediatric age group, the principle of *resection of* [illegible]

Even though the period of renal artery occlusion required for repair has usually been less than 15 min, the authors subject their patients to *systemic hypothermia* [2] for added safety

Regardless of which reconstructive technique is to be employed, the surgical approach of preference is anterior and transperitoneal A generous midline or paramedian incision is used The transverse incision, or flank approach, has been found to be less desirable After the peritoneal cavity has been entered and explored, the transverse colon and omentum are lifted up and out of the wound, and placed on the anterior thorax The small bowel is similarly eviscerated and packed off to the right The latter maneuver may be facilitated, and exposure about the renal arteries later enhanced, by division of the ligament of Treitz The abdominal aorta is then exposed by incising the posterior peritoneum in the avascular area between the root of the small bowel mesentery on the right and the inferior mesenteric vein on the left. The dissection is then carried proximally until the left renal vein and the renal arteries are identified It is helpful at this point to use the previously performed aortogram for direction in terms of the number and locale of the individual renal vessels It is possible to expose the main renal arteries throughout their

[2] See Part 6, Chap 16 Editor

[illegible] aorta, should be used.

Arterial anastomoses are performed using fine sutures and interrupted technique. In the repair of a renal artery in a 4-year-old, where the stenosis involved too long a segment for use of the two previously mentioned techniques, the authors have used *longitudinal section* and then the *placement of an onlay autogenous venous graft* to provide for a normal lumen The portion of vein was obtained from the patient's internal iliac system

In the treatment of adult stenosis, where the etiologic factor is most commonly focal arteriosclerotic change, the method of choice is either *endarterectomy or division of the vessel distal to the stenosis, and reimplantation on the adjacent aortic wall* These techniques are best suited to the patient with a localized process involving the immediate area of the arterial origin and with a thin-walled, normal adjacent aorta Because the aorta is generally thickened and abnormal in the entire general area of the renal vessel, the alternate reconstruction technique of *bypass grafting* has been used most commonly.

If reconstructive surgery is to be performed in relation to the abdominal aorta itself, as in the management of aortoiliac occlusive disease or arteriosclerotic abdominal aneurysm, then the bypass technique becomes by far the most practical Cus-

6 Patients with demonstrable arteriosclerotic disease, especially of the aorta and iliac channels, plus hypertensive disease

7. Hypertensive patients with a history suggestive of a renovascular accident.

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RENAL ARTERY ANEURYSM

Aneurysms of the renal artery are not common. The literature records an incidence of 0.1 to 0.15 per cent based on autopsy studies, or 1 per cent of all aneurysms (Ippolito and LeVeen). The total number of cases reported as of 1959 by Glanton and associates was 143. The lesion may be secondary to arteriosclerosis, trauma, infection, or a congenital defect of the arterial wall, and may be classified as a true or false aneurysm The majority of the aneurysms are saccular in type. The post-stenotic dilatation, typically present distal to an arterial stenosis, should not be classified as an aneurysm, the anatomic and physiologic features are obviously entirely different Case reports have shown no predilection concerning sex of the patient or side of involvement Lesions have been reported from childhood through advanced age, but most of them have been diagnosed in the 40- to 60-year-old group. The aneurysm may occur in the main renal artery, in the renal parenchyma, or at any point between, but most of them occur in the distal main channel or just beyond the primary bifurcation (McLelland)

A survey of the literature reveals that flank pain and hematuria are the most common symptoms Hypertension occurs in only 15 to 20 per cent of patients, and in some instances there may be no relationship between the aneurysm and the pressure elevation A palpable mass will be noted in about 25 per cent of patients, and microscopic, if not gross, hematuria can be detected in about 35 per cent.

Complications of renal artery aneurysm include rare instances of renal infarction and, more commonly, rupture The rupture may be into adjacent retroperitoneal tissues with a high immediate mortality, or into the adjacent vein with the resulting complication of renal arteriovenous fistula

Although of the reported cases many were [illegible] often seen with splenic artery aneurysms, may be seen on the plain x-ray films. Unfortunately, less than one-third of the lesions present this finding (Pastor). The pyelogram may show distortion of the kidney, and direct evidence of renal artery abnormality will be demonstrated on the aortogram.

Treatment, with few exceptions, has been *nephrectomy*. The opportunity of resection and reconstruction with renal preservation should be taken advantage of when there is a technically favorable lesion in the main renal artery If the aneurysm has been obstructing the arterial flow and hypertension has resulted, a favorable result in terms of blood pressure can be anticipated. It should be remembered, however, that often lesions do not produce hypertension, and that elevated blood pressure may not be due to the aneurysm. The data would indicate caution in relating hypertension to a given renal artery aneurysm, and, therefore, conservatism in predicting its relief by surgical eradication of the lesion

RENAL ARTERY THROMBOSIS

Thrombosis of a renal artery may occur secondary to *preexisting local* disease in the ultimately occluded channel, or may be due to an *embolic phenomenon* (Ben-Asher, Fishberg). *Total infarction of the kidney* does not result in hypertension, but *subtotal infarction* or *ischemia* may give rise to malignant hyperten- [illegible] per cent of patients, *occult* or frank hematuria. Renal infarction may be unilateral, *bilateral*, total, or segmental

Diagnosis of the acute lesion will be directed *by the onset of acute flank pain*, the finding of *hematuria, and often* leucocytosis. Intravenous pyelography will show variable results [illegible] retrograde pyelogram should be normal The diagnosis of renal arterial occlusion should be *made possible* in most cases by a carefully *performed* aortogram.

When *hypertension* results from the renal *ischemia, relief* from surgery *may* be anticipated, as in the patient of Wilkey and associates Treatment will usually consist of nephrectomy for main renal artery thrombosis, or of subtotal *resection* for partial ischemia.

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Diagnosis of the acute lesion will be directed by the onset of acute flank pain, the finding of hematuria, and often leucocytosis. Intravenous pyelography will show variable results, depending upon the total degree of infarction, but often there will be nonvisualization. Initially the retrograde pyelogram should be normal. The diagnosis of renal arterial occlusion should be made possible in most cases by a carefully performed aortogram.

When hypertension results from the renal ischemia, relief from surgery may be anticipated, as in the patient of Wilkey and associates. Treatment will usually consist of nephrectomy for main renal artery thrombosis, or of subtotal resection for partial ischemia.

PART 13

Pulmonary hypertension and pulmonary heart disease (cor pulmonale)

1

Pathology of chronic cor pulmonale

DAVID M. SPAIN

A strict definition of chronic cor pulmonale limits it to *that form of hypertrophy of the right side of the heart (with or without congestive failure) that develops secondary to diseases of the lung, pulmonary blood vessels, chest cage, or primary pulmonary hypertension* A wider use of the term includes *those forms of pulmonary hypertension that occur secondary to mitral stenosis and certain forms of congenital heart disease*. The development of all forms of chronic cor pulmonale is mainly dependent upon the degree and duration of the elevation of the pressure in the pulmonary vascular bed Therefore, the term *pulmonary hypertensive heart disease* is preferable Many classifications have been proposed for chronic cor pulmonale None fulfill all the basic pathogenetic, functional, and clinical needs because gaps in our knowledge still exist concerning the relative importance of neurohumoral, structural, and functional mechanisms in the control of vasomotor tone and blood flow in the pulmonary vascular bed

The proper appreciation of pulmonary hypertension requires knowledge not only of those alterations in the lungs, pulmonary vessels, heart, and associated structures that precede the onset of the hypertension, but also of the changes in the heart, pulmonary blood vessels, and other viscera that occur as sequelae to the effects of the hypertension

THE PULMONARY VASCULAR BED

The pulmonary arterial system is divided into four major segments. The largest vessels are the *elastic arteries*, with an external diameter usually greater than 1,000 μ The walls of these arteries contain considerable elastic tissue and smooth muscle. The next category is comprised of the *muscular arteries*, with a luminal range of 1,000 to 100 μ in diameter. Their walls are composed of a circular muscular layer enclosed in internal and external elastic membranes The next smaller segments are the *arterioles*, which run a very short course and do not contain muscle. These are usually less than 100 μ in diameter The walls consist of an endothelial layer supported by a single elastic membrane. Finally, there are the *capillaries*, which have neither muscle nor elastic tissue and consist of endothelium surrounded by basement membrane. It is of significance that the muscular arteries, which are the main resistance vessels, have only a very thin muscular coat For this reason, the vasomotor, reflex, or other functional influences on the muscular coat can play only a relatively small part in increasing resistance to the flow of blood and consequently in the production of pulmonary hypertension. Therefore, *mechanical and other functional factors are more important in controlling the pressure in the pulmonary arterial system than is the case in the systemic circulation* The interplay of these mechanical and functional factors, however, is complex. Thus, several characteristics of the pulmonary vascular bed serve to distinguish it from the systemic vascular bed and also influence the significance of the anatomic alterations secondary to pulmonary disease. *These are its great distensibility, large reserve, and thin musculature.* These features contribute to the maintenance of the pulmonary vascular bed as a low-pressure system. Pulmonary

hypertension, the basic functional cause for the development of cor pulmonale, differs from systemic hypertension in that it is possible, in the overwhelming majority of instances, to identify some underlying organic alterations that serve to explain rationally the pathogenesis of the increase in blood pressure. In systemic hypertension, mainly because of the well-developed musculature in the arteriolar system and its response to a wide variety of neurohumoral mechanisms and agents, organic alterations that serve to explain the process rationally are less frequently encountered

POST-MORTEM IDENTIFICATION OF COR PULMONALE

The recognition of cor pulmonale at autopsy is almost entirely dependent upon the evaluation of the degree of *hypertrophy of the right ventricular myocardium.* The right ventricle at birth has a relatively greater muscle mass than the left because in utero the pulmonary circulation is maintained as a high-resistance system for the purpose of shunting the blood of the right side of the heart away from the lungs into the systemic circulation via the ductus. After birth, upon closure of the foramen ovale and ductus arteriosus, the ventricular relationships are altered, so that in adult life, the left ventricle contains the preponderance of muscle mass Ordinarily, in the adult, *any excess in diameter of the right ventricular wall over 5 mm is regarded as hypertrophy* The evaluation of this hypertrophy as being entirely the result of pulmonary hypertension is usually dependent upon the elimination of other causes of cardiac hypertrophy such as systemic hypertension (with chronic left ventricular failure), valvular disease, myocarditis, nutritional defects, etc However, the simple determination of the thickness of the right ventricle in itself as the means of diagnosing cor pulmonale at post-mortem examination is sometimes inadequate. If this measurement is the only consideration, then a number of cases will be missed. A more exact and inclusive method is to weigh the left ventricle with the attached septum separately from the right ventricle after dissection made according to the technique described by Fulton et al. Consideration must also be given to the effects of dilatation of the heart on the thickness of the ventricle, and also to debilitating disease process, in which the heart mass as a whole may be reduced in weight. Because of the variations in the anatomic methods for the determination of cor pulmonale, differences exist in the reported incidence of this condition, even when diseases with the same underlying pulmonary diseases are studied. The condition of the pulmonary vasculature may be helpful, but correlation between these changes and the degree of right-sided heart hypertrophy is variable.

CLASSIFICATION OF CAUSES OF PULMONARY HYPERTENSION

Pulmonary hypertension is classified as *primary or secondary.* In *primary hypertension*, the mechanisms are unknown, and well-authenticated cases in adults are rare (see Causes of Pulmonary Hypertension, below). In adults, most forms of pulmonary hypertension occur secondary to diseases of the chest cage, lungs, or pulmonary vessels (see Classification of Pulmonary Disease—Causes of Chronic Cor Pulmonale, below). A modified functional classi-

Causes of Pulmonary Hypertension

- I Primary pulmonary hypertension (pathogenesis unclear)
  - *A* Childhood type
  - *B* Adult type
- II Secondary pulmonary hypertension
  - *A* Congenital heart disease with left-to-right shunts
  - *B* Acquired heart disease (mitral stenosis)
  - *C* Pulmonary disease
    - 1 Chest cage and pleura (kyphoscoliosis, thoracoplasty)
    - 2 Parenchymal disease (emphysema, interstitial fibrosis)
    - 3 Pulmonary vascular disease (thromboembolism, schistosomiasis)

Classification of Pulmonary Disease—Causes of Chronic Cor Pulmonale

- I Anatomic or functional alterations in thoracic cage
  - *A* Kyphoscoliosis, thoracoplasty
  - *B* Obesity syndrome
  - *C* Fibrous pleural envelope
- II Anatomic alterations in the pulmonary vasculature
  - *A* Main pulmonary arteries (thrombus, extrinsic pressure)
  - *B* Muscular arteries and arterioles (thromboembolism, arteritis, schistosomiasis)
  - *C* Anomalies, malformations, or tumors of pulmonary vessels
  - *D* Venous obstruction
- III Anatomic alterations in the bronchi and pulmonary parenchyma
  - *A* Idiopathic, primary, or large-lung emphysema
  - *B* Secondary obstructive emphysema (bronchiectasis, pneumoconiosis, asthma, tuberculosis)
  - *C* Diffuse interstitial inflammation and fibrosis (sarcoid, beryllhosis, interstitial fibrosis)

fication suggested by Mack subdivides cor pulmonale caused by pulmonary disease into two main groups, *type 1*, in which the pulmonary diseases are associated with *chronic diffuse obstructive emphysema*, and *type 2*, in which the pulmonary diseases also contain *pathologic processes localized in or about the blood vessels*. It is also recognized that there may be no rigid distinction between the two groups, in that the features of both may be present in any individual case. The significance of this classification is that in hypertension associated with pulmonary disorders, some of the underlying disturbances may be reversible, whereas in the type based on organic changes of the vasculature, reversibility is rare.

The mechanisms by which congenital heart disease leads to pulmonary hypertension are related basically to persistent communications between the pulmonary and systemic circuits, usually with a left-to-right shunt. In these situations, abnormal alterations exist in pressure and flow relationships. These vary with the type of congenital malformation and the underlying state of the pulmonary vascular bed. The relative importance of flow as related to pressure changes in the production of the pulmonary hypertension is as yet not entirely resolved. In rheumatic mitral stenosis, there is the additional factor of an increase in left atrial pressure, which increases the distending pressure in the various pulmonary vessels. However, no linear correlation exists between the degree and duration of the mitral stenosis, the level of pressure in the pulmonary circuit, and the secondary changes in the pulmonary vessels.

PULMONARY MECHANISMS THAT PRODUCE HYPERTENSION

In pulmonary disease, those structural alterations of the pulmonary vascular bed that are of primary significance consist of varying degrees of obstruction, compression, and obliteration of the capillary bed in ventilated lungs, luminal narrowing, occlusion, or distortion of the smaller muscular pulmonary arteries, precapillary arterioles, and veins; and changes in the immediate tissue environment of the vessels, which tend to alter transmural pressure and thus diminish distensibility of the vessels. The distensibility potential, large reserve, and relative lack of musculature of the pulmonary vascular bed are key factors in the proper evaluation of the relative effects of structural versus functional alterations in the production of pulmonary hypertension.

The primary lung diseases that affect the pulmonary vascular bed are numerous. A study of over 10 years ago reported the findings of 100 consecutively autopsied cases of cor pulmonale and revealed the incidence of underlying "primary" pulmonary disease shown in Table 13-1. More recent studies of consecutively autopsied cases of cor pulmonale reveal that *idiopathic, obstructive, or large lung emphysema has become absolutely and relatively the most important cause of cor pulmonale, whereas bronchiectasis, a disappearing disease, has decreased as an underlying pulmonary mechanism.*

The significance of pulmonary tuberculosis as a cause of cor pulmonale is difficult to evaluate, since the types of cases vary from one institution to another. In recent years, the chronic forms of tuberculosis have declined, and consequently the long-standing cases with fibrosis and secondary emphysema are not seen so frequently. In past years, the incidence of cor pulmonale in tuberculosis was related to the healing process, with emphysema produced as a consequence of fibrosis in areas of widespread bronchogenic dissemination.

There is no direct relationship between cor pulmonale and the degree of parenchymal destruction. In certain areas of the country, in-

TABLE 13-1 BASIC UNDERLYING PULMONARY CONDITIONS IN 100 CONSECUTIVE NECROPSIES ON PATIENTS WITH COR PULMONALE

Underlying pulmonary condition	*No of cases*
Emphysema (diffuse, obstructive)	52
Bronchiectasis (diffuse, bilateral)	9
Bronchial asthma	6
Silicosis and silicotuberculosis	6
Tuberculosis.	6
Kyphoscoliosis. .	1
Thoracoplasty and tuberculosis	5
Primary pulmonary arteriolosclerosis	1
Diffuse interstitial fibrosis. .	5
Schistosomiasis	1
Foreign-body emboli (morphine addiction)	1
Multiple pulmonary emboli with organization	2
Pulmonary artery thrombosis	2
Scleroderma. . . .	1
Boeck's sarcoid	2

dustrial dust exposures and pneumoconiosis are of great importance as causes of cor pulmonale. There appears to be an increase in the incidence of diffuse interstitial inflammation and fibrosis of the lung. In some of these cases, cor pulmonale occurs.

In the preantibiotic period, a study of 200 consecutive autopsied cases of *bronchiectasis* that had not been treated with surgery revealed that in 38 cases, the bronchiectasis was bilateral and diffuse, and involved the smaller ramifications of the bronchial tree. Twenty-five of these 38 cases had hypertrophy of the right ventricle. In none of the other cases was cor pulmonale noted. This would indicate that *pulmonary disease usually must be diffuse and bilateral in order to produce significant structural alterations in the pulmonary vascular bed that will eventuate in cor pulmonale.* In these 25 cases, it is important to note that *emphysema* was a prominent feature. Liebow et al. (1949) demonstrated *large bronchopulmonary arterial communications* in advanced bronchiectasis. These shunts, which allow a high-pressure system to communicate with a low-pressure system, are probably not of prime importance in the causation of pulmonary hypertension because, as already noted, cor pulmonale does not occur in bronchiectasis unless the process is widespread and accompanied by emphysema.

Notably absent from the list of pulmonary conditions that cause cor pulmonale are those which produce solid areas of carnification or organization of varying portions of the parenchyma of the lung (organized pneumonia, radiation pneumonitis with fibrosis, lipoid pneumonia, etc.). Although structural alterations of the pulmonary vascular bed in such areas are profound, the fact that there is no parenchymal function (ventilation) present renders these changes of little clinical or physiologic significance. The granulation tissue in these areas is mostly supplied by the bronchial arterial system, and any alteration in flow would not be reflected in the pulmonary circuit. Only in those cases where the anatomic extent of lung involvement is so great as to deplete the vast reserve of the pulmonary vascular bed, are clinical or abnormal physiologic manifestations present. It should be noted that, provided the contralateral lung is normal, pneumonectomy does not produce a significant rise in pulmonary pressure.

The most important and basic underlying pulmonary disease that compromises the pulmonary circulation is emphysema. This includes the so-called primary, idiopathic, or large-lung type, the pathogenesis of which is still in dispute, as well as the forms of obstructive emphysema that are secondary to other primary pulmonary disease such as bronchial asthma, silicosis, etc. Anatomically, it is difficult, if not in most instances impossible, to recognize emphysema definitively unless it has entered the destructive phase, in which *the alveolar walls are disrupted, with coalescence of the alveolar spaces.* This alteration of the alveolar walls is the key to the morphologic alterations in the pulmonary vascular bed in emphysema. The alveolar walls are destroyed, thinned, disrupted, and at times thickened with fibrous tissue, inflammatory exudate, or an increase in smooth muscle. These alterations directly affect the capillary bed, as well as some of the larger vessels (veins and arteries).

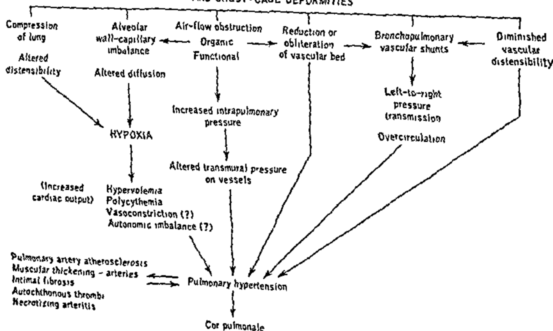
Difficulties in quantitatively measuring changes in the capillary bed are numerous. The techniques that are so advantageously applied to the study of the larger vessels and bronchopulmonary communications require injection pressures so high as to make them unrealistic for the study of the capillary bed. Furthermore, it is difficult to simulate the intraalveolar pressure relationships that exist during life. However, some information can be gained from a poor substitute, and that is the study of hyperemic or congested emphysematous lungs at post mortem in the human being. It should be remembered that studying sections of the lung in this way, relative to pressure, flow, and ventilatory interrelationships, is analogous to studying one flat still film in a three-dimensional motion picture. Yet, despite the errors and limitations inherent in such a study, it is possible to demonstrate certain alterations and abnormal relationships.

In comparison with the congested normal lung, there is *a diminution in the number of hyperemic capillaries in many areas of the emphysematous alveolar walls.* In the normal lung, the distribution of the congested capillaries is regular, whereas in emphysema it is irregular. A relatively larger number of precapillary arterioles and smaller arteries is seen in the alveolar walls. Some of these thin-walled distended vessels may even be capillaries. Thus, many of the red blood cells passing

through these vessels in the alveolar walls are now quite distant from the alveolar capillary interface. In the normal lung, the capillaries usually are only distended to the caliber of the diameter of one red blood cell The inclusion of terminal bronchiolar passages in the distended emphysematous spaces accounts for the incorporation of greater numbers of larger vessels in the walls of the emphysematous air sacs Many of the capillaries (distended or not) are removed from intimate contact with the alveolar interface by fibrous tissue, smooth muscle, or inflammatory exudate To make the situation more complex, seemingly adequately perfused alveolar walls may exist in areas where, from a structural point of view, there would appear to be insufficient ventilation In contrast, one may observe meager perfusion in alveoli that would appear to have been better ventilated This is partly the consequence of the varied interplay of mechanical alterations which, in some areas, distend portions of the lung and, in others, may partially compress adjacent pulmonary parenchyma Also present are elongation, distortion, and compression of the larger vessels (veins and arteries) that course through the emphysematous areas These in turn may be supplying or draining capillaries in areas of pulmonary parenchyma that are relatively normal The variety of these changes is great from one portion of the lung to another and exists even in the smaller pulmonary subunits Variation and lack of homogeneity are characteristic This condition of *varied alveolar wall–capillary imbalance* is one of the basic consequences of the structural alterations that occur in emphysema The implications of this, relative to proper interpretation and evaluation of various function tests, are obvious

In addition to the direct anatomic alterations on the capillary, arteriolar, and small arterial and venous bed, the indirect effects of the altered pressure relationships that occur in the environment of these vessels as a consequence of emphysema have serious implications In emphysema, as well as in other pulmonary conditions, profound effects on function (hypoxia, etc.) alter the pulmonary blood flow, volume, and tension well in advance of the destructive effects of the disease on the morphologic characteristics of the vascular bed.

The relative importance of the *direct structural* versus the *indirect functional effects* on the pulmonary circulation may be illustrated by such conditions as kyphoscoliosis, complete unilateral thoracoplasty, and the obesity syndrome In these conditions, in time, pulmonary hypertension develops which may be severe enough to produce cor pulmonale, yet in some cases of kyphoscoliosis as well as in unilateral thoracoplasty, the emphysema and the struc-



tural changes in the blood vessels are entirely inadequate to account for the cor pulmonale. In the obesity syndrome, of course, there is no emphysema or any other notable primary structural alteration in the pulmonary vascular bed. Situations of this sort indicate that such factors as hypoxia, hypervolemia, etc., are perhaps the primary factors in the development of pulmonary hypertension rather than the structural alterations that develop later—in the destructive and irreversible phases of pulmonary disease processes. In *kyphoscoliosis* and in *unilateral thoracoplasty*, unilateral kinking of vessels is probably not a factor because the secondary vascular manifestations of pulmonary hypertension are equally reflected in both lungs.

In an entirely different area of lung disease, *the diffuse interstitial, inflammatory, and fibrotic processes*, cor pulmonale also occurs. In this group, which includes nonspecific interstitial fibrosis, berylliosis, sarcoid, certain forms of pneumoconiosis, etc., the blood vessels throughout the lung are encased in an environment of fibrous tissue, inflammatory exudate, granulomas, and edema. This reduces the distensibility of the vascular bed. The alveolar-capillary block and diminished ventilation of the lung in these conditions contribute important functional disturbances that favor the onset of pulmonary hypertension.

A general scheme of the pathogenesis of pulmonary hypertension in pulmonary disease is presented in the diagram, "Pathogenesis of Cor Pulmonale in Chronic Pulmonary Disease and Chest-cage Deformities" (page 13-7).

CHANGES IN THE VASCULAR BED

Direct structural involvement of the pulmonary arterial system by *thrombi, embolic carcinoma, polyarteritis*, or *schistosomiasis* obviously increases the resistance to the flow of blood. Plexiform vascular arrangements have been observed in these conditions, similar to those noted in pulmonary hypertension secondary to congenital cardiovascular disease. Whether these plexiform vascular arrangements are bypasses, vascularized granulation tissue, or shunts is not always entirely clear.

In cor pulmonale, the most consistent and prominent morphologic changes in the pulmonary vascular bed are actually secondary manifestations to the alterations in blood flow, volume, and tension produced by the various causes of chronic cor pulmonale. These changes consist basically of *atherosclerosis in the larger elastic arteries, hypertrophy (or at least apparent thickening) and the development of a longitudinal muscle layer of the muscular arteries, and fibrosis of the intima in the smaller arteries and precapillary arterioles*. The evaluation of muscular thickening is difficult because of the artifact produced by contraction.

Other changes consist of autochthonous *arterial thrombi* and *necrotizing arteritis or arteriolitis*. These thrombi may become so unrecognizable through organization as to be confused with arteriosclerosis (Fig. 13-1).

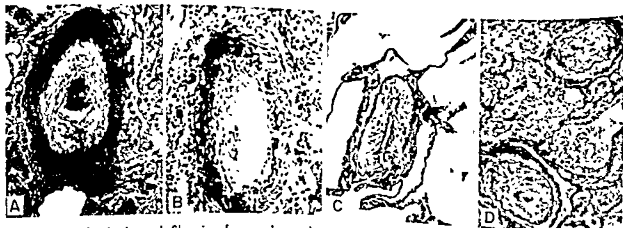


Fig. 13-1. A. Intimal fibrosis of muscular pulmonary artery (secondary to pulmonary hypertension). B. Necrotizing lesion in muscular pulmonary artery in a case of advanced mitral stenosis. C. Muscular thickening of a small muscular artery in a case of emphysema with pulmonary hypertension. D. Canalized and organized thrombi in muscular pulmonary arteries.

This has unfortunately led to the erroneous classification of some cases as primary pulmonary hypertension. The necrotizing vascular lesions in the past have been misinterpreted as specific consequences of rheumatic fever but more recently are regarded as one of the nonspecific effects of high pressure on the pulmonary vascular circuit. These alterations in turn may contribute to the increased vascular resistance to blood flow.

In pulmonary hypertension associated with congenital heart disease, the severity of the changes in the pulmonary blood vessels parallels the degree of pulmonary hypertension. In contrast to this, in pulmonary hypertension caused by lung disease in adults, there is poor approximation between the severity of the hypertension and the extent of the secondary vascular changes. Care must be taken not to confuse morphologic alterations in the arteries as a result of aging with those specifically caused by hypertension.

In the adult, the average weight of the heart in autopsied cases of chronic cor pulmonale is 450 Gm, with variations between 350 and 800 Gm. The average thickness of the right ventricular wall is 0.8 cm, with extremes of 0.6 and 1.5 cm. The left ventricle, at times, may exhibit a minimal to moderate degree of hypertrophy that cannot be related to other diseases. This may be partially explained by the effects of hypoxia on the heart and possibly by the appearance of large bronchopulmonary venous shunts in emphysema (see Chap. 3). Fibrosis of the myocardium is not a prominent feature and, when present, can usually be accounted for on the basis of a frequently coexistent coronary atherosclerosis. Mural thrombi are occasionally present in the right atrium. Also, in some instances, there may be notable dilatation of the tricuspid valve ring.

When failure occurs in chronic cor pulmonale, the liver and spleen are the constant sites of varying degrees of both acute and chronic congestion. Cardiac cirrhosis of the liver, although generally uncommon, occurs more frequently in this than in other forms of heart failure.

UNEXPLAINED PULMONARY HYPERTENSION

Cases in which there are no demonstrable changes to account for the pulmonary hypertension are referred to as *primary pulmonary hypertension*. Until more information is forthcoming concerning the pathogenesis of these cases and the reflexes that influence pulmonary vascular tone, these should be referred to as cases of *unexplained* pulmonary hypertension. Reported cases of so-called primary pulmonary hypertension in which vascular occlusive lesions, arteritis, persistence of fetal-type arteries, abnormal communications between bronchial and pulmonary circulation, and ingrowth of intimal fibrous tissue into the pulmonary arteries from Sperrarterien should be classified as secondary pulmonary hypertension. When these are eliminated, very few authenticated cases remain. The few well-documented cases are more frequent in females, children, and young adults. This is in contrast to the secondary form of pulmonary hypertension seen in pulmonary disease. Considerable confusion in regard to primary pulmonary hypertension continues to exist because it is difficult to evaluate the primacy of certain vascular lesions. Experimentally, fibrin and even nitrogen bubble emboli in the pulmonary vessels may produce end-stage lesions that could be interpreted either as being secondary to hypertension or as being evidence of primary pulmonary arteriosclerosis. In the human being, healed thromboemboli may be indistinguishable from primary alterations in the vascular wall. On the one hand, arteritis may give rise to thrombi, and on the other thromboemboli may produce arteritis. A proper interpretation of the correct sequence in which these lesions develop is essential for the proper evaluation of the causes and classification of pulmonary hypertension.

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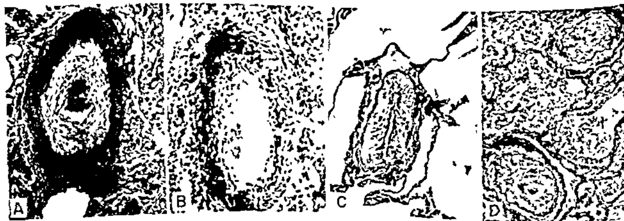


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occupational factors to emphysema, bronchitis, and asthma However, since such a high proportion of cases of emphysema and bronchitis have their origin in industrial causes, a specific relationship with occupational hazards will probably be demonstrable in a high proportion of cases

The prevalence of cor pulmonale as a factor in the causation of disability will ultimately be proved higher than in many statistics, this becomes self-evident when one notes that autopsies are made in only a small proportion of individuals who died from occupation-related disease Death may also occur from some other cause while cor pulmonale may have been present as a component factor in disability Only serial and detailed examination of individuals routinely exposed to hazardous substances while employed would reveal the true prev
trial dise

There
is on the increase This may be partly explained by the fact that ultrahazardous occupational exposures have been eliminated in most civilized communities Formerly, such excessive exposures may have destroyed workmen before they had a chance to develop cor pulmonale. Now they survive and the repetitive injury to their pulmonary vasculature results in cor pulmonale. It has also been suggested that air pollution, which ultimately is of industrial origin, may be a material factor in the causation of bronchitis and cor pulmonale (Flint, 1954). This suggestion merits serious further exploration, for if it is true, persons other than workmen are involved. It is certainly true that in the so-called neighborhood cases of *berylliosis*, cor pulmonale has been a prominent cause of death, even among children

More cases of cor pulmonale will be detected in life if the rigid standard, requiring a right ventricular wall of at least 5 mm in thickness for a diagnosis of cor pulmonale, be reconsidered. In view of the fact that the thickness of the right ventricular wall can be materially influenced by the degree of distention of the chamber, the mural thickness cannot serve as a rigid criterion of cor pulmonale A simple calculation will suffice to illustrate that the state of contraction or distention of the right ventricle is an important determinant of the thickness of the ventricular wall. As the muscle mass remains constant, whether in a state of contraction or distention, it should be apparent

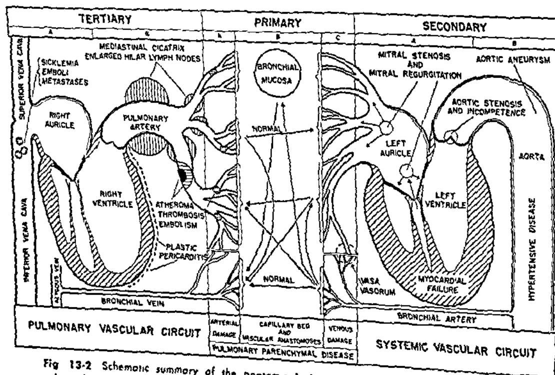


Fig 13-2 Schematic summary of the anatomic factors involved in the pathogenesis of cor pulmonale.

Occupational aspects of cor pulmonale

G. W. H. SCHEPERS

ETIOLOGY AND PREVALENCE

Occupational factors are responsible for a large proportion of all the cases of cor pulmonale which develop in adults In some countries, where children are employed in hazardous industries, cor pulmonale of occupational origin has occurred even in adolescents Statistics about the true incidence of industrial cor pulmonale are scanty During the 20 years from 1931 to 1950 the percentage of cases in which cor pulmonale was the cause of death in the pneumoconioses was variously reported as being from 14 8 per cent (Middleton, 1936) to 50.2 per cent (Gooding, 1946) These variable figures are partly due to the greater or lesser prevalence of tuberculosis and of various complications as causes of death This is because, under the heading of pneumoconiosis, greater or lesser numbers of cases of silicosis, anthracosis, or asbestosis were included It is well established that asbestosis yields a high proportion of deaths from cor pulmonale Silicosis in the advanced stages is terminated by cor pulmonale in inverse proportion to the prevalence of tuberculosis. In the majority of instances, cor pulmonale is, however, a terminal factor also in cases of tuberculosis complicating silicosis. Among anthracotic patients, the percentages of deaths due to cor pulmonale vary, apparently according to the free silica content of the coal dust and the relative prevalence of progressive massive fibrosis In anthracotic patients with tuberculosis (Wells, 1954b), cor pulmonale is a significant additional factor in the causation of death. On the contrary, the heart is seldom involved in persons with siderosis unless massive fibrosis has occurred. In the latter cases, the silicotic disease is more important than the siderotic process in the genesis of cor pulmonale, though some synergism apparently occurs. Cor pulmonale tends to be more prevalent among the siderosilicotic patients than among those with silicosis only.

In addition to the classical forms of pneumoconiosis, emphysema, bronchitis, asthma, and bronchiectasis may contribute a significant number of cases of cor pulmonale which have their ultimate origin in occupational factors Emphysema has gained increasing recognition not only as a pulmonary complication of the pneumoconioses, but also as a primary result of exposure to dusts and other injurious respiratory hazards (Mayer et al., 1956). Bronchitis and asthma may develop as occupation-related diseases (Schepers, 1955b), while bronchiectasis occurs much more rarely as a primary sequel to industrial exposures As emphysema, bronchitis, and asthma have increased in incidence, especially among those members of the community who are gainfully employed, it is of interest to note that cor pulmonale is cited as a complication in a comparatively high proportion of cases. Among 45 cases of emphysema studied, Griggs et al (1939) reported cor pulmonale in 29 per cent This is the lowest incidence cited, and the authors did not comment separately on bronchitis or asthma Cor pulmonale has been reported much more frequently in relation to emphysema, bronchitis, and asthma by other workers. The various statistics have not yet been analyzed to define the causal relationship of

tinal lymph nodes resulting from inhaled dusts, kinking and stenosis of the pulmonary artery by *chest deformities* due to industrial accidents, and showers of emboli arising from venous damage at remote points may similarly *lead to cor pulmonale*. Secondary cor pulmonale, of course, can be a sequel to disease of the systemic vascular circuit which results in cardiac failure and which may have its origin in occupational factors

Usually, occupational cor pulmonale occurs in a chronic form, and in most instances it arises insidiously. In some cases, however, the cardiac reaction to the pulmonary disease develops more rapidly and dramatically. This result is particularly likely in association with those lung states in which relatively acute impairment of the breathing surface is brought *about* (e.g., *chemical inflammatory* states, edema, vascular necrosis)

The various stages of cor pulmonale (Fig. 13-3) are all typical for occupational *cor pulmonale*. *Stage I* is usually *not* diagnosable unless special precautions are taken to elicit signs which are suggestive of it. This stage is usually also reversible, provided the causative lesion in the lungs is amenable to therapeutic or spontaneous amelioration. Stage II is associated with symptoms and is more readily recognizable as a clinical entity because of its characteristic radiographic appearances and electrocardiographic accompaniments *Stage III* is that which is usually encountered at autopsy when death has been due to the cor pulmonale. Figure 13-4 *represents a typical* example. Features of this case which merit special recognition are hypertrophy of the myocardium, of the trabeculae carneae, and of the papillary muscles of the right ventricle; moderate distention of the right ventricle; prominence of the pulmonary outflow tract, which is covered by fat; enlargement of the pulmonary artery, the internal diameter of which equals that of the aorta; marked distention of the right atrium with prominent muscular ridges; incompetence of the tricuspid valve. In the case shown in Fig. 13-4, in addition to the extensive destruction of the vascular bed, there was concomitant hypertrophy of the bronchial arterial system.

PATHOGENESIS

Anatomic mechanisms which *may induce* cor pulmonale *may be classified as shown in* Table 13-2.

The occupational factors which involve the *pulmonary arterial trunk* and main vessels are relatively few. *An aneurysm of the aorta* or the *sinus of Valsalva* which results from *occupational trauma* may subsequently compress the pulmonary trunk. Gross *thoracic deformities*, which may result from occupationally *derived sternal, vertebral*, or costal damage, may effectively impair the pulmonary circulation by compressing or kinking the *main trunk*. *The pulsatile excursions* of the main pulmonary vessels may also be impaired through external fixation by *incarcerating lymph nodes, as in silicosis* and tuberculosilicosis, or by *mediastinitis*, such as may be sequential to a bron-

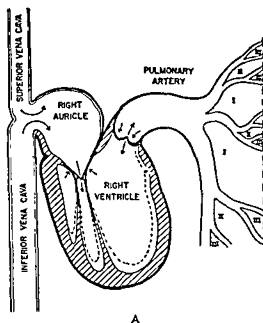


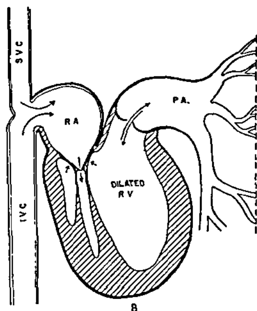
Fig. 13-4. Advanced cor pulmonale in a victim of asbestosis. A. Horizontal section through the ventricles at their level of maximal size. Hypertrophy of the right myocardium, papillary muscles, trabeculae carneae, and dilatation of the ventricle. B. Dissection of the base of the heart to display the dilated right auricle with its prominent muscle ridges, the relative incompetence of the tricuspid valve, and enlargement of the pulmonary outflow tract and pulmonary artery.

that the mural thickness may vary through a range of plus or minus 100 per cent, according to whether the surface area of the ventricle is doubled or halved by distention or contraction.

PATHOLOGIC ANATOMY

In respect of its anatomic features, cor pulmonale does not differ materially in the industrial series from cor pulmonale of nonoccupational origin. Inasmuch as it usually occurs in the older age group, the occupation-related disease affects a heart which may simultaneously be the seat of degenerative changes resulting from hypertension, arteriosclerosis, coronary stenosis, etc. In these respects, cor pulmonale of occupational origin may differ from cor pulmonale sequential to congenital factors.





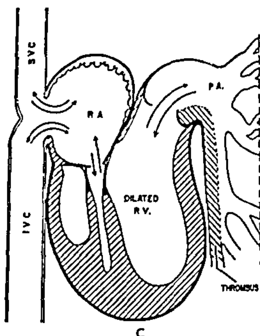


Fig. 13-3. Summary of the anatomic changes which occur in the progression of cor pulmonale from its subclinical to its clinical state.

It occurs not uncommonly that in the occupational variety, there is *hypertrophy of both the right and the left ventricle.* Whether both hypertrophic changes are ascribable to the occupational factor has not yet been demonstrated satisfactorily. In cor pulmonale accompanied by an increased cardiac output, there is a logical explanation for the associated hypertrophy of the left ventricle If simultaneously some unrelated systemic disease elevates the left ventricular pressure, hypertrophy of the left myocardium once more is explicable But neither systemic disease nor increased cardiac output may be present to account for the left ventricular enlargement. There is at least some experimental evidence to indicate that certain inhaled siliceous dusts of the submicron amorphous variety may elevate the systemic blood pressure at the same time that the pulmonary pressure rises in response to the parenchymal changes.

As an occupational disease, cor pulmonale usually occurs as the primary variety due to disease originating in and topographically restricted to the lungs (Fig. 13-2) Much less frequently, cor pulmonale may also be sequential to tertiary mechanisms promoted by occupational factors. Thus, cicatrizing medias-

paratively inert inhaled substances, such as coal dust, may bring about the same effect through the massive infiltration of the perivascular adventitia by koniophores (Fig. 13-5C). Obstruction of the vessel lumen may be thus produced without any appreciable collagen deposition However, fibrosis usually accompanies the process of cellular proliferation around the blood vessels (Fig 13-5D).

Changes which occur in the walls of blood vessels are usually less dramatic than the foregoing but may be equally disabling. As a result of sustained elevation of the pulmonary arterial pressure the muscular coat may hypertrophy considerably. It is difficult, however, to gage when this process has attained a pathologic degree, as the thickness of the muscular layer is largely influenced by the state of contraction or relaxation in which the pulmonary vessels were fixed at death In silicotic patients, however, there seems to be a predominant tendency for the blood vessels to be in a relatively spastic state. Arterial spasm of even a moderate degree may elevate the pulmonary tension considerably. The causal relationship between medial myohypertrophy and cor pulmonale is more directly apparent when such muscular hyperplasia occurs regionally (Fig 13-6A).

Degeneration of the muscle layer must inevitably affect its efficiency as a transit system for the perfusion of parts of the lung parenchyma supplied by it (Fig. 13-6B). While such fibrotic changes often occur in pneumoconiosis in the absence of any locally demonstrable causative agent, foreign



Fig 13-5. Perivascular *adventitial* changes which may obstruct the pulmonary circulation A. Multilaminated concentric collagen deposits around a medium-sized pulmonary blood vessel in the lung of a worker occupationally exposed by inhalation *to chrome-*, nickel-, and berryllium-containing dusts. *Weigert*, X250. B Exuberant proliferation of *the* elastic laminae around a blood vessel in the lung of an asbestos worker who died of cor pulmonale Weigert, X250. C Dense collections of coal-dust-filled koniophores surrounding atrophic blood vessels in the lungs of a coal miner who died of cor pulmonale Hematoxylin *and eosin*, X8 D Stenosed blood vessel within an encircling zone of dust-laden cells, foreign particles, and collagen bundles, in an asbestos worker with fatal cor pulmonale Mallory, X260.

TABLE 13-2. PATHOGENESIS OF COR PULMONALE: ANATOMIC LESIONS OF OCCUPATIONAL ORIGIN

Pulmonary artery	*Intrapulmonary vessels*		*Alveolar mural capillaries*
	Arteries	*Veins*	
Compression: Aneurysm Thoracic deformity	Perivascular lesions: Inflammation Fibrosis Infiltration	Perivascular lesions: Inflammation Fibrosis Infiltration	Impaired aeration: Bronchiolar and bronchial obstruction Bronchospasm Emphysema Atelectasis Pneumonia
Fixation: Mediastinitis Incarcerating lymph nodes Impairment: Tumor Trauma Thrombosis	Medial changes: Myohypertrophy Myosclerosis Vasospasm Intimal damage: Proliferation Thrombosis Atheroma Embolism	Medial changes: Myosclerosis Intimal damage: Proliferation Thrombosis Edema	
		Bronchopulmonary shunts: Azygos obstruction	Normal aeration: Impaired perfusion Obstructing membrane Alveolar mural infiltration Alveolar mural sclerosis Thrombosis Hyperplasia Shunts
	Panvascular involvement: Incorporation Destruction Distortion Compression	Panvascular involvement: Incorporation Destruction Distortion Compression	

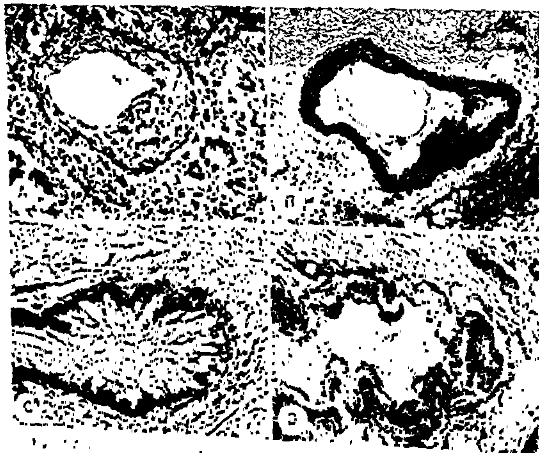
chial or esophageal erosion by silicotic lymph nodes, or which may result from thoracic trauma with mediastinal hemorrhages. *Pulmonary tumors* of occupational origin, such as those resulting from the inhalation of chromic, cobaltic, arsenical, nickel, and asbestos dusts, rapidly involve the mediastinal lymph nodes and thus precipitate cor pulmonale As a final event in long-standing elevated pulmonary tension, *thrombosis* is a factor in aggravating preexisting cor pulmonale or even in initiating this cardiac complication

By far the largest number of illustrations of specific industrial causes of cor pulmonale may be found among the lesions of the intrapulmonary blood vessels. The perivascular reactions are both the more conspicuous and the more important among these. During exposures to toxic or irritating substances, such as *chemical fumes and gases*, intrapulmonary inflammatory changes of variable severity and chronicity result The usually dispersed localization of these reactions results in widespread involvement of multiple intrapulmonary vessels This inflammatory state may by itself induce acute cor pulmonale, which not infrequently is the immediate cause of death in such individuals More usually the cardiac complication follows only after a prolonged interval, and the impairment of the pulmonary blood vessels is then caused by *perivascular fibrosis.* This may take the form of collagen hyperplasia (Fig 13-5A) or may result from proliferation of the elastic lamina (Fig 13-5B) Even com-

which are quite insufficient to sustain the circulation to the appropriate pulmonary sector (Fig 13-7C). The siliceous particles may often be demonstrated by polarized-light microscopy within these proliferated tissues *Endarteritis obliterans* of equally extraneous origin is particularly likely to occur in the lungs of employees in asbestos industries (Fig. 13-7D) At low-power magnification, the responsible mineral agent is frequently undetectable in the intimal zone, but coarser asbestos bodies may be found in the vascular adventitiae. Oil-immersion microscopy may then be resorted to, and the asbestos fibers will usually be demonstrable in the intima as well.

In vessels whose lumens have not been completely occluded by intimal proliferation, the process may be completed by *thrombosis* The occurrence of such clots and their subsequent dislodgement and reimpaction as *emboli* further along the blood vessel induce marked *vascular spasm*, which may be a material factor in precipitating a more advanced stage of cor pulmonale. Such episodes occur rather frequently in industrial personnel who are transferred from one inhalation hazard to another.

Bronchopulmonary vascular shunts are not specific for the occupationally determined cases of cor pulmonale. The pneumoconioses, and particularly asbestosis, tend, however, to foster their development.



... and proliferation of the intima ... vessels by intimal proliferation. A. Cellular infiltration of a small blood vessel in the lung of a beryllium worker who died of cor pulmonale. Weigert, ×330. B. Proliferation of vascular intima fills in sulci formed in a medium-sized blood vessel as a result of stenosis by surrounding cicatricial tissue. Ceramic worker with fatal exposure to tridymite. Weigert, ×35 C. A few vascular channels are all that remain of the blood vessel lumen in the lung of a diatomaceous-earth worker who died of cor pulmonale (cristobalite exposure). Weigert, ×230. D. Distortion of a blood vessel, which is the seat of endarteritis obliterans of asbestotic origin. Weigert, ×250.

bodies are not infrequently discovered within the vessel wall (Schepers, 1955a). They may be present there without apparently causing any pronounced local reaction (Fig 13-6C). On the other hand, the presence of isolated foreign agents, such as asbestos fibers, may induce a conspicuous response, which when widely dispersed in the vessels of the lung, undoubtedly may serve as an explanation for coexistent cor pulmonale.

Occlusion of the vascular lumens may occur on a widespread scale in the occupational pulmonary diseases, but may be frequently missed because the identity of the blood vessels is soon obliterated Vessels of all calibers may be simultaneously affected, or the brunt of the damage may fall selectively on smaller or on larger vessels The lesser arteries and venules are affected most severely in the occupational diseases in which highly active irritant substances constitute the specific hazard Thus the lungs of victims of metallic poisoning frequently display widely disseminated intimal proliferation in minute pulmonary vessels of a degree sufficient to create a significant impediment to the pulmonary circulation (Fig 13-7A). In these occupational diseases, however, intimal proliferation may affect even relatively large blood vessels In such cases, the explanation not infrequently seems to lie in the associated distortion and narrowing of the blood vessel through external cicatricial forces (Fig. 13-7B). In addition to the cellular phases of the intimal proliferation, inhaled foreign substances, such as quartz dust, cristobalite, or tridymite, provoke collagen formation The lumen of the vessel eventually becomes reduced to one or more minute canals,

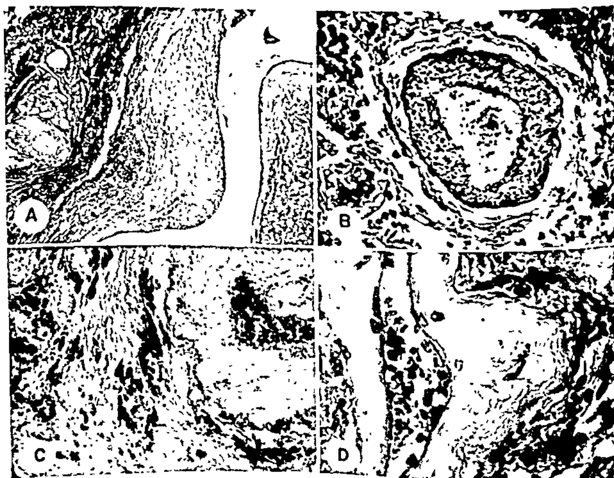


Fig. 13-6. Mural damage in pulmonary blood vessels A Segmental myohypertrophy in a silicotic patient who died of cor pulmonale. Hematoxylin and eosin, ×65. B. Regional degeneration and fibrosis of the vascular muscular layer in a siderotic patient. Mallory, ×350 C. Talc bodies embedded in the wall of a blood vessel display iron-staining properties of their sheaths. Prussian blue, ×160. D. Asbestos body embedded in the wall of a small blood vessel, where its presence provoked a pronounced reaction. Cause of death was cor pulmonale. Mallory, ×800.

lung lobe in which all blood vessels have been occluded. The capacity of several of these lesions to induce cor pulmonale is self-evident. In *progressive massive fibrosis* of coal workers, this cardiac complication is particularly prevalent.

In addition to distortion, compression, or obliteration of blood vessels in such areas of massive fibrosis, there is the added factor of loss of capillary bed. In these cruder examples, there is loss both of aeration and of perfusion. Cor pulmonale may, however, occur through impaired respiratory activity at the capillary level with or without decreased aeration. In those pneumoconiotic conditions, such as talcosis, in which the bronchi sustain the brunt of the damage so that their lumens become occluded, the role of impaired aeration as a factor in eliminating the function of the capillaries is self-evident (Fig. 13-9B). More usually the main damage occurs at the bronchiolar level, and there usually is an associated *bronchiolar spasm*. The latter probably is a material factor in the genesis of some forms of emphysema which occur in industrial workers and which later become associated with cor pulmonale.

One essential change induced by *emphysema* is impaired aeration. In view of the tremendous reserve of the lungs, the emphysema would have to be of a very advanced grade before cor pulmonale could follow merely as a result of reduced aeration of mural capillaries. In emphysema of occupational origin,

Fig. 13-9. [illegible] sive fibrosis [illegible] lung of a magnetite miner who died of cor pulmonale [illegible] of the pulmonary circulation. A. Massive fibrosis [illegible] represents an entire lobe. Hematoxylin and eosin, ×2. B. Perivascular infiltration and fibrosis caused by inhaled tremolite talc dust in a paper mill employee. Hematoxylin and eosin, ×35. C. Emphysema with interspersed atelectasis and [illegible] cor pulmonale [illegible] a person [illegible] [illegible]atite ore miner with [illegible] walls in the lungs of [illegible] stitutes on [illegible] The cell layer con[illegible] and the mural capillaries. Mallory, ×350.

ous pneumoconioses The relationship between the cor pulmonale and the occupational exposures may then be the more readily demonstrated. In the pneumoconioses resulting from inhaled metallic substances, the unit lesions are more often than not perivascular in distribution and effectively embarrass the pulmonary circulation because of their prevalence (Fig. 13-8A). Even in areas of diffuse or massive granulomatous reaction in which some vascular proliferation occurs, the newly formed capillaries soon acquire a collagen sheath which effectively eliminates such channels as agents for the maintenance of the respiratory function (Fig. 13-8B) The relationship of the silicotic nodule to the pulmonary blood vessels is usually not easily recognized once hyalinization has been completed Elastic tissue staining may, however, demonstrate the skeletons of such blood vessels even in mature nodules (Schepers, 1955a). In the earlier phases of silicosis, and particularly in siderosilicosis, it is frequently possible to demonstrate the perivascular distribution of the nascent nodule (Fig 13-8C). Even in asbestosis, there may be relatively large focal collections of fibrous tissue around distorted and stenosed blood vessels (Fig 13-8D).

Vascular destruction or obliteration occurs on a much grander scale in tuberculosilicotic fibrosis, carnification of unresolved pneumonic or atelectatic pulmonary segments or lung lobes, or when neoplasia complicates a pneumoconiotic process A fibrotic mass, which measures 5 to 7 cm in maximal diameter (Fig 13-9A), may represent a completely devitalized

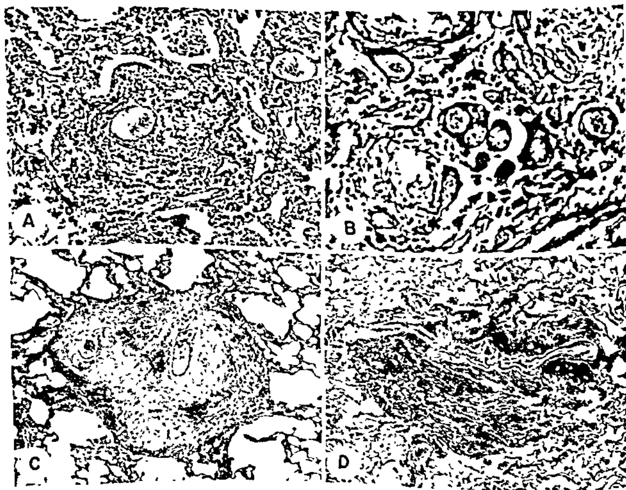
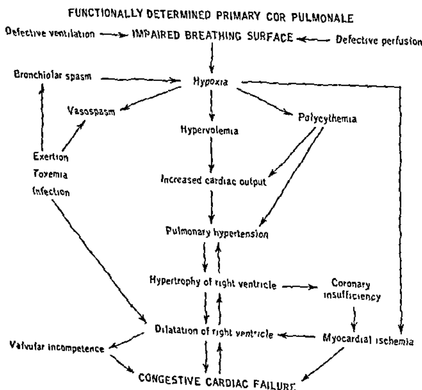


Fig. 13-8. Incarceration of blood vessels within specific pneumoconiotic lesions A. Pulmonary granuloma in the lung of a uranium machinist has enveloped a minute blood vessel. Mallory, ×175. B Pericapillary collagenosis in a granulomatous area of the lung of a deceased person occupationally exposed to beryllium, tungsten, and other metallic dusts. Mallory, ×350 C. Perivascular distribution of the evolving silicotic nodule in a silica flour employee who died of cor pulmonale. Hematoxylin and eosin, ×35 D. Focal fibrosis in asbestosis involving a medium-sized blood vessel which is distorted and stenosed. Mallory, ×65.

stitial pulmonary fibrosis, therefore, necessarily terminates in cor pulmonale.

In addition to the devascularizing processes, various occupational diseases of the lungs, but especially asbestosis, promote the excessive proliferation of capillary plexuses and the development of short-circuiting vascular shunts Such changes add further to the embarrassment of the circulation, much of the blood circulating through the affected areas failing to become oxygenated

Numerous other subtle mechanisms operate at the alveolar plane While some mechanisms would lead to cor pulmonale by direct obstruction to blood flow, others achieve their effect on physiologic principles. *Hypoxia* (see *diagram below*) not only exerts its action on the chemoreceptors of the lung, but also influences the brain stem, pulmonary blood vessels, bronchioles, bone marrow, and myocardium. The resultant hypervolemia and increased cardiac output are therefore responsible for the pulmonary hypertension, cardiac hypertrophy, dilatation, and ultimate failure It is doubtful, however, whether cor pulmonale ever occurs as an occupation-related disease purely on such a physiologic basis There usually is such abundant concomitant pulmonary disease that the role of obstructive factors cannot be negated. *As a clinical disease, the cor pulmonale associated with the pneumoconioses tends to be predominantly of the low-output type,* though it should be conceded that the high-output variety occurs with sufficient frequency in industrial workers to support the suggestion that, in some cases, functional factors may be of paramount significance in the genesis of the disease



cor pulmonale ensues the more readily because there frequently is associated focal atelectasis, while there may be obliteration of other alveoli by processes of impaction of koniophores in the alveoli. The emphysema no doubt also subjects the capillaries to tension and thus impedes the circulation through them. The emphysema is frequently associated with mural thickening and fibrosis, which additionally occlude alveolar capillaries (Fig. 13-9C).

An obstructing membrane interposed between normally perfused alveolar capillaries and normally aerated alveoli would frustrate the respiratory function and thereby induce cor pulmonale. Such a membrane may be of extraneous origin but may also be the result of proliferation of the mural epithelium. The latter occurs relatively frequently in persons exposed to *beryllium* (Fig. 13-9D). Through infiltration of the alveolar walls by cells or collagen (Fig. 13-10A and B), the capillary plexuses may be eliminated. The devascularization process may be completed by thrombosis. These changes are particularly common in Shaver's disease, diatomaceous earth pneumoconiosis, and in exposures to tridymite and cristobalite.

Even in the presence of advanced interstitial fibrosis, capillaries may yet survive over the surfaces of the newly deposited stromal elements. This is the more likely when the reticulum or excessive elastic tissue rather than collagen (Fig. 13-10C and D) constitutes the skeletal framework. Not every case of inter-

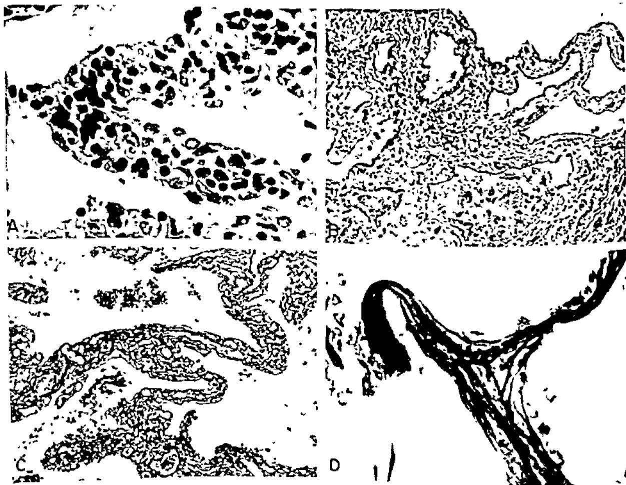


Fig. 13-10. Alveolar mural damage which affects the capillary bed. A. Cellular infiltration of the alveolar walls mechanically occludes the mural capillary plexuses in the lungs of an employee of a brass and copper alloying industry. Hematoxylin and eosin, ×800. B. Interstitial mural fibrosis which creates a barrier between the alveolar air and deeply buried capillaries. Exposure to asbestos dust. Mallory, ×175. C. Reticulin hyperplasia with preservation of capillary network in the lung of an iron miner. Foote, ×1,700. D. Proliferation of elastic fibrils in a thickened alveolar wall which has not resulted in impairment of the capillary plexuses. Asbestos miner. Weigert, ×1,700.

and still containing cartilage, the nature of the bronchial *Sperrarterie* becomes even more evident The "longitudinal" muscle fibers show considerable development These longitudinal fibers, if thoroughly investigated, reveal a spiraling course in the vessel wall, and project into the lumen Such anatomic arrangement may be considered to be the cause of the contraction of the blood vessel (Fig 13-11B)

Such anastomoses were still encountered at a level of bronchi of 1.2 to 1 3 mm in diameter (Fig. 13-12) The outer diameter of the anastomosis is around 100 μ It should be noticed that the branches of the pulmonary artery which anastomose with the bronchial *Sperrarterie* are not of the muscular but of the elastic type The author's studies with the vinyl cast showed such anastomoses to exist in the vascular system of the mediastinal pleura

Abundant sensory nerves and ganglion cells were found in the bronchial *Sperrarterie* by the silver-impregnation method. Such anatomic structure may be compared with that found in the glomus at the periphery of the extremities In the lung, this structure plays an important role in the control of the pulmonary blood pressure (Fig 13-13).

The pressure relationship between the bronchial and pulmonary arterial systems, as well as the flow in the anastomoses between both,

f dilata-

As the blood pressure in the bronchial artery is several times higher than that in the pulmonary artery, the blood flow at the anastomosis will take the direction which is shown in Fig 13-14B In normal lungs, however, the blood volume of the bronchial artery is minimal in comparison with the total pulmonary blood flow As a volume factor, its influence upon respiratory function may be disregarded. It is doubtful whether such minimal volume of bronchial blood flow would contribute to the nutrition of the alveolar wall via the anastomosis or not According to the pressure difference of both arteries, the peripheral resistance of the pulmonary artery will increase at the periphery Accordingly, the blood flow of the pulmonary artery in this area is somewhat decreased Liebow et al (1950) suggested that in an affected lung, the increased bronchial arterial flow draining into the pulmonary artery via the developed anastomoses would prevent the pulmonary blood flow to the affected area and

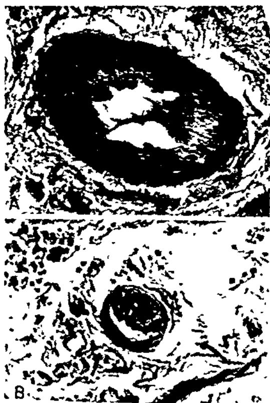


Fig. 13-11. A So-called *bronchial Sperrarterie. It is apparent that the wall is composed of inner longitudinal and outer circular muscle fibers. The media exhibits muscle fibers which run spirally in the vessel wall. The injected gelatin is seen as a bridge in the lumen* Normal lung. B *Bronchial Sperrarterie along the smaller bronchi. Inside one layer of the circular muscle fibers in the media, the intimal thickening, which exhibits many transversely cut longitudinal muscle fibers, protrudes into the lumen on one side.* Normal lung.

would prevent venous admixture This mechanism, however, is difficult to imagine under normal conditions, where the *Sperrarterien* are occluded and no blood flows through the anastomoses If, however, the difference in blood pressure of the two arteries changes considerably, the collaterals will open.

The anastomoses between the pulmonary and the bronchial arteries in the normal lung have been widely discussed by many investigators in the past Reports by Miller (1950), who denies the existence of such anastomoses, are mainly based on experimental data *in dogs* The author's own observations in dogs showed no bronchial *Sperrarterien* in this species, and no anastomoses between the two arterial systems could be demonstrated. Presumably, the

3

The role of bronchial circulation in chronic pulmonary diseases

TAKASHI NAKAMURA

It has been pointed out that in chronic pulmonary diseases, the increased development of bronchial blood vessels or the development of precapillary anastomoses between bronchial arteries and branches of the pulmonary artery plays an important role in the circulation. It has been felt that when cardiopulmonary dynamics is studied in these diseases, the role of the bronchial circulation cannot be disregarded.

For several years, the author and his coworkers have studied the morphology and physiology of the bronchial vascular system; they have succeeded in measuring the bronchial flow.

OUTLINE OF BRONCHOPULMONARY CIRCULATION; *SPERRARTERIE*

As already known, the *bronchial arteries* originate from the aorta or intercostal arteries, enter each lung along the main bronchus, supply blood to the bronchial wall and the adjacent structures along the bronchial tree, and finally terminate at the periphery of the bronchial tree. During its course, the *peribronchial capillary bed* is formed. The capillary blood becomes venous and drains into the pulmonary vein. Only the blood of the bronchial artery providing the hilar region will return to the azygos and hemiazygos veins via the extrapulmonary bronchial vein (or pleurohilar vein). *The venous blood draining from the peribronchial capillary bed mixes with arterial blood* of the pulmonary capillaries, reaches the pulmonary vein, and finally returns to the left atrium. This represents *a postcapillary anastomosis* between the bronchial and pulmonary venous circulations. There are, in addition, important anastomoses between the bronchial and the pulmonary arteries at the precapillary level.

At present, there are two concepts of the anastomoses between the bronchial artery and pulmonary artery. The German school maintains that there are anastomoses between these systems of arteries, while the American and English schools deny them. In order to clarify this controversy, serial sections on several normal adult lungs were made to study the blood vessels along the bronchial tree. *This revealed that clear arterial anastomoses exist between them.* When a normal bronchial artery was followed from the hilar region to the periphery of the lung, a layer of longitudinal muscle fiber directly below its endothelium appeared in the peripheral branches. These longitudinal muscle fibers are rarely found in the branches of the bronchial arteries along large bronchi, if found, they appear as a single layer of muscle cells sometimes protruding as a crescent into the lumen. Such longitudinal muscle fibers become more prominent around middle-sized and smaller bronchi with an internal diameter of less than 3 mm. The walls of bronchial arteries in this area consist of circular muscle fibers in the media and longitudinal muscle fibers in the subintima (Fig. 13-11). This ramification was called *bronchial Sperrarterie* by Hayek.[1] In the walls of smaller bronchi with a caliber of less than 1.5 mm

[1] The nearest English translation is "bronchial blocking artery" or "bronchial barrier artery."

ured by Bruner and Schmidt, who used the bubble flowmeter technique Using the same principle, similar results have been reported by the author, who has also designed a new method for the measurement of the bronchial blood flow in human lungs

In chronic lung disease, the anastomoses between the bronchial and the pulmonary arteries become more extensive, in other words, the anastomoses between the two arterial systems are in a functional status. Then, bronchial arterial flow drains into the pulmonary arterioles under a high pressure, which is only slightly lower than that of the aorta Consequently, the blood flow in the pulmonary capillaries is greater than that which reaches the pulmonary artery from the right heart. If the capillary blood flow of the pulmonary alveoli and right cardiac output are separately measured, the bronchial blood flow can be obtained by their difference

Some of the blood from the right heart will, however, return to the left atrium without coming in contact with the alveolar air, because of the existence of arteriovenous capillaries This represents *a true venous mixture* and might be termed an "anatomic venous mixture" In chronic pulmonary diseases, this process is remarkably increased (Wilson et al, 1951) As such venous shunt carries the blood which leaves the lung without coming in con-



Fig. 13-13. A. *Terminal reticulum, nerve bundles, and thick medullated sensory fibers which are discovered around the bronchial Sperrarterie* (cut tangentially) Silicotic lung, silver impregnation *t*, terminal reticulum, *b*, thick medullated *sensory fibers, n, nerve bundles* B *Ganglion*, closely relat*ing to the bronchial Sperrarterie* Silicotic lung Silver impregnation *g*, ganglion

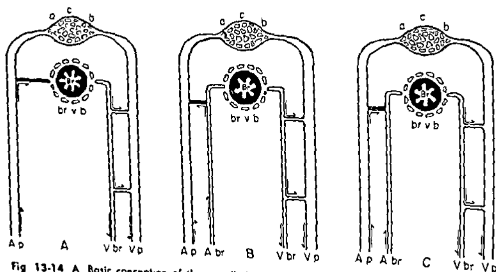


Fig 13-14 A Basic conception of the so-called Sperrgefass (blocking artery) by Hayek (arteriovenous shunt) B *Diagram illustrating arterioarterial anastomosis (author's conception).* C. Suggested *diagram illustrating* contraction of bronchial artery *a c b*, alveolar capillary bed, *A p.*, *pulmonary artery, A br*, bronchial artery, *Br., bronchus; br v.b*, bronchial vascular bed, *V.p*, pulmonary vein, *V br*, bronchial vein.

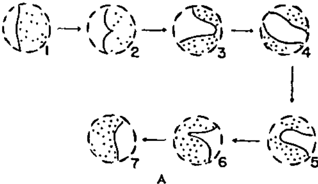
connections between the pulmonary system and the bronchial system of dogs occur at the capillary level.

Vinyl cast studies of diseased *human lungs* clearly demonstrate the presence of precapillary anastomoses through *Sperrarterien*, and anastomoses through dilated capillary vessels appearing like arterial anastomoses *In other words, in human lungs, both anastomoses between the system of the bronchial artery and that of the pulmonary artery, and capillary anastomoses exist, while in dog lungs, only the latter are found*

Aside from these intimate collateral relationships of the bronchial and pulmonary circulation within the parenchyma of the lung, there exists a communication at the pulmonary hilum. It is an anastomosis between the extrabronchial veins (pleurohilar veins) and pulmonary veins. The pulmonary veins communicate with the systemic venous system by way of this passage. Its significance has already been pointed out by the author, by Gilroy et al., and by Hurwitz et al.

BRONCHIAL BLOOD FLOW

Method of Measurement. The bronchial arterial blood flow in the dog has been successfully meas-



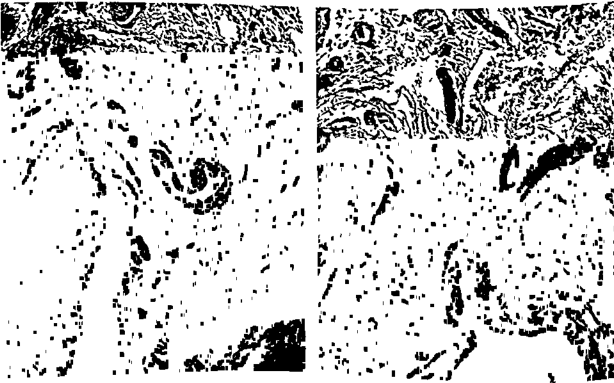


Fig. 13-12. A and B. A small branch of the bronchial artery (*bronchial Sperrarterie*), along the smallest bronchus with cartilage, sends a thin-walled branch towards the submucosal layer Normal lung. C The small branch of the bronchial artery shown in A and B finally anastomoses to the pulmonary artery at the lower end of the figure. Normal lung.

was found impossible to perform alveolar air sampling in patients with severe obstruction of the air passages (pulmonary emphysema, etc.), because of variability in the determination of alveolar air.

The maximum error in determination of the cardiac output by the Fick's method should not be above 5 per cent, if the error in measurement of O_2 in the arterial and mixed venous bloods is only 0.1 vol per cent, when arteriovenous O_2 difference is 4 vol per cent. In the measurement of pulmonary capillary blood flow, on the other hand, an error of 0.5 mm Hg of alveolar CO_2 pressure corresponds to about 10 per cent of blood flow. Therefore, in the determination of the value of the bronchial blood flow, the above analytic error should be taken into consideration. After considering these points, however, it may still be concluded that in several patients with chronic pulmonary diseases, a large quantity of bronchial blood flows into the lungs.

New Way of Measuring Bronchial Blood Flow by the Dye-dilution Method. At present, the dye-dilution method is employed in the author's laboratory for the measurement of bronchial blood flow. The method consists of a simultaneous measurement of left and right ventricular outputs with two cardiac catheters.

One catheter is introduced into an antecubital vein and advanced until the tip lies in the main pulmonary artery. Another catheter is advanced through a second vein until its tip lies in the superior vena cava. A Cournand needle is inserted into the bronchial artery. Three to four cubic centimeters of Evans blue or Bromsulphalein is rapidly injected into the superior vena cava. Simultaneously, blood is sampled in small test tubes from the pulmonary artery and brachial artery every 1 to 2 sec. In sampling from the pulmonary artery, the end of the catheter is inserted into a negative pressure chamber, with a pressure of about 200 mm Hg below atmospheric, and the small test tubes in the chamber are automatically rotated. Dye concentration in serum is measured by means of an electrophotometer, and two dye-dilution curves are inscribed.

The curves drawn from the brachial artery and pulmonary artery should measure the outputs of the left and right ventricles, respectively. Then, the difference between the two should be attributed to an increase of the bronchial blood flow.

Experiments were attempted at first in normal dogs, and the outputs of the left and right ventricles were found to be practically identical (Table 13-3). Then a shunt was made between the left subclavian and the left pulmonary artery in other dogs, and the outputs were measured by the dye-dilution method. At the same time, blood flow through the shunt was directly measured by means of a bubble flowmeter placed in the course of the shunt and by bleeding from the anastomotic

TABLE 13-3 COMPARISON OF LEFT AND RIGHT VENTRICULAR OUTPUTS BY THE DYE-DILUTION METHOD IN NORMAL DOGS

Dog No	Body weight, kg	Ventricular output, L/min		Left − right, L/min
		Left	Right	
11	14.5	1.68	1.70	−0.02
12	11.5	2.26	2.50	−0.24
13	25.0	3.45	3.58	−0.13
14	11.0	2.31	2.15	+0.16
16	12.0	1.03	0.99	+0.04
19	10.5	1.26	1.26	0
20	16.2	1.21	1.22	−0.01
25	35.0	6.27	6.24	+0.03

TABLE 13-4 LEFT AND RIGHT VENTRICULAR OUTPUTS BY THE DYE-DILUTION METHOD AND SHUNTED BLOOD FLOW IN DOGS WITH LEFT SUBCLAVIAN-PULMONARY ARTERIAL ANASTOMOSIS

Dog No	Body weight, kg	Ventricular output, L/min		Left − right, ml/min	Bubble flowmeter method, ml/min	Bleeding method, ml/min
		Left	Right			
16	12.0	1.95	1.83	120	110	185
17	15.0	2.63	2.26	370	480	500
19	10.5	1.40	0.99	410	480	500
25	35.0	5.46	5.05	410	480	340

tact with alveolar air, it will not be included in the pulmonary capillary blood flow measured here. Therefore, if the value obtained by taking the anatomic venous mixture from the right cardiac output is subtracted from the value of the pulmonary capillary blood flow, a more correct blood flow of the bronchial circulation will be given. The anatomic venous mixture ratio can be calculated as a ratio of the left cardiac output, which is the total sum of right cardiac output plus bronchial blood flow. Its blood flow should also be calculated in relationship to the left cardiac output.

The blood flow of the bronchial artery can be obtained by the following equation.

$$BF = PCF - \left[CO - \frac{(CO\ BF)X}{100}\right]$$

$$BF = \frac{PCF}{1 - \frac{X}{100}} - CO$$

where BF = bronchial blood flow
CO = right cardiac output
PCF = pulmonary capillary blood flow
X = anatomic venous mixture ratio

The expression "bronchial blood flow" indicates that part of the arterial blood flow of the bronchial artery which mixes with blood of the pulmonary arterioles through precapillary anastomoses.

A Method to Measure Pulmonary Capillary Blood Flow. The method developed by Bing et al (1947) was adopted. Capillary blood CO_2 concentrations upon entering and leaving the alveoli may be determined by the equilibration method of CO_2 in the alveoli. Pulmonary capillary blood flow can be calculated by Fick's principle

$$\begin{Bmatrix}\text{Pulmonary}\\ \text{capillary}\\ \text{blood flow}\end{Bmatrix} = \frac{CO_2 \text{ output (ml/min)}}{\begin{bmatrix}\text{concentration of blood } CO_2\\ \text{entering the alveoli (vol \%)}\\ -\text{ concentration of blood } CO_2\\ \text{leaving the alveoli (vol \%)}\end{bmatrix}}$$

In order to calculate the concentration of CO_2 of the capillary blood which leaves the alveoli, CO_2 in the alveoli is measured by the end-inspiratory method of Haldane and Priestley. In order to calculate the concentration of CO_2 of the capillary blood which enters the alveoli, three kinds of mixed gas consisting of 4, 5, and 6 per cent of CO_2 to O_2, respectively, are deeply inhaled after full expiration. The succeeding breath is then held for 8 to 10 sec in order to obtain an equilibrium between the capillary blood and alveolar gas. The patient is finally instructed to exhale forcefully. The CO_2 in the alveoli is then measured. If three values of alveolar CO_2, after inhalation of three CO_2 mixtures, agree within 0.2 per cent, respectively, the blood which enters the alveoli and the alveolar air are considered to be well equilibrated. The average is taken. These two kinds of alveolar CO_2 tensions, corresponding to alveolar gas equilibrated with blood which enters and leaves the alveoli, are converted to concentration of blood CO_2 by *Singer's nomogram*, using arterial and venous oxygen saturation, pH, and hematocrit.

Method to Measure Anatomic Venous Admixture (Katori). Anatomic venous mixture can be measured by nullifying the venous mixture which is caused by poorly ventilated alveoli following inhalation of pure O_2 gas for over 20 min to replace N_2 in the alveoli. Venous mixture which still exists after inhalation of pure O_2 for a long time is the blood flow in the nonventilated alveoli. In other words, it is the real venous shunt.

After the subject has breathed pure oxygen during cardiac catheterization, arterial blood is sampled from the indwelling needle in the brachial artery and is immediately centrifuged anaerobically under low temperature. The plasma O_2 tension is measured polarographically by a mercury electrode. Oxygen tension in the alveoli is measured by the *Haldane-Priestley method*. The arteriovenous O_2 difference is determined from the blood gas analysis by the *Van Slyke manometric method*. The following equation may be obtained

$$\begin{Bmatrix}\text{Anatomic venous}\\ \text{mixture ratio}\end{Bmatrix} = 100 - \left(\frac{Y}{Y - G} \times 100\right)$$

where Y = arteriovenous O_2 difference (vol %)
G = (alveolar PO_2 − arterial PO_2) × B
B = O_2 volume dissolved in blood under 1 mm Hg O_2 tension at 37.0°C (vol %)

CRITICISM OF THE METHOD. At present, it is undoubtedly difficult to determine accurately the bronchial blood flow in man without surgery. The above method involves a few difficulties: (1) impossibility of a simultaneous measurement of pulmonary capillary blood flow and cardiac output in a steady condition, and (2) necessity of operator's skill and subject's cooperation for the CO_2 equilibration in the alveoli and for alveolar air sampling. In the author's experiments, all measurements were always performed under the same basal conditions, evaluated through O_2 consumption and respiratory quotient, in order to maintain the patient's state as steady as possible. The determination of alveolar air, after prolonged training of the subject, was repeatedly carried out in order to obtain constant values. Consequently, it

was found impossible to perform alveolar air sampling in patients with severe obstruction of the air passages (pulmonary emphysema, etc.), because of variability in the determination of alveolar air.

The maximum error in determination of the cardiac output by the Fick's method should not be above 5 per cent, if the error in measurement of O_2 in the arterial and mixed venous bloods is only 0.1 vol per cent, when arteriovenous O_2 difference is 4 vol per cent. In the measurement of pulmonary capillary blood flow, on the other hand, an error of 0.5 mm Hg of alveolar CO_2 pressure corresponds to about 10 per cent of blood flow. Therefore, in the determination of the value of the bronchial blood flow, the above analytic error should be taken into consideration. After considering these points, however, it may still be concluded that in several patients with chronic pulmonary diseases, a large quantity of bronchial blood flows into the lungs.

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20	16.2	1.21	1.22	−0.01
25	35.0	6.27	6.24	+0.03

TABLE 13-4. LEFT AND RIGHT VENTRICULAR OUTPUTS BY THE DYE-DILUTION METHOD AND SHUNTED BLOOD FLOW IN DOGS WITH LEFT SUBCLAVIAN-PULMONARY ARTERIAL ANASTOMOSIS

Dog No.	*Body weight, kg*	*Ventricular output, L/min*		*Left − right, ml/min*	*Bubble flowmeter method, ml/min*	*Bleeding method, ml/min*
		Left	*Right*			
16	12.0	1.95	1.53	120	110	155
17	15.0	2.63	2.26	370	450	300
19	10.5	1.40	0.99	410	450	300
25	35.0	5.46	5.05	410	450	340

tact with alveolar air, it will not be included in the pulmonary capillary blood flow measured here. Therefore, if the value obtained by taking the anatomic venous mixture from the right cardiac output is subtracted from the value of the pulmonary capillary blood flow, a more correct blood flow of the bronchial circulation will be given The anatomic venous mixture ratio can be calculated as a ratio of the left cardiac output, which is the total sum of right cardiac output plus bronchial blood flow. Its blood flow should also be calculated in relationship to the left cardiac output.

The blood flow of the bronchial artery can be obtained by the following equation:

$$BF = PCF - \left[CO - \frac{(CO\ BF)X}{100} \right]$$

$$BF = \frac{PCF}{1 - \frac{X}{100}} - CO$$

where BF = bronchial blood flow
CO = right cardiac output
PCF = pulmonary capillary blood flow
X = anatomic venous mixture ratio

The expression "bronchial blood flow" indicates that part of the arterial blood flow of the bronchial artery which mixes with blood of the pulmonary arterioles through precapillary anastomoses.

A Method to Measure Pulmonary Capillary Blood Flow. The method developed by Bing et al (1947) was adopted. Capillary blood CO_2 concentrations upon entering and leaving the alveoli may be

CO_2 in

can be

$$\left\{ \begin{array}{l} \text{Pulmonary} \\ \text{capillary} \\ \text{blood flow} \end{array} \right\} = \frac{CO_2 \text{ output (ml/min)}}{\left[\begin{array}{l} \text{concentration of blood } CO_2 \\ \text{entering the alveoli (vol \%)} \\ -\text{ concentration of blood } CO_2 \\ \text{leaving the alveoli (vol \%)} \end{array} \right]}$$

In order to calculate the concentration of CO_2 of the capillary blood which leaves the alveoli, CO_2 in the alveoli is measured by the end-inspiratory method of Haldane and Priestley. In order to calculate the concentration of CO_2 of the capillary blood which enters the alveoli, three kinds of mixed gas consisting of 4, 5, and 6 per cent of CO_2 to O_2, respectively, are deeply inhaled after full expiration The succeeding breath is then held for 8 to 10 sec in order to obtain an equilibrium between the capillary blood and alveolar gas. The patient is finally instructed to exhale forcefully. The CO_2 in the alveoli is then measured. If three values of alveolar CO_2, after inhalation of three CO_2 mixtures, agree within 0.2 per cent, respectively, the blood which enters the alveoli and the alveolar air are considered to be well equilibrated. The average is taken These two kinds of alveolar CO_2 tensions, corresponding to alveolar gas equilibrated with blood which enters and leaves the alveoli, are converted to concentration of blood CO_2 by *Singer's nomogram*, using arterial and venous oxygen saturation, pH, and hematocrit.

Method to Measure Anatomic Venous Admixture (Katori). Anatomic venous mixture can be measured by nullifying the venous mixture which is caused by poorly ventilated alveoli following inhalation of pure O_2 gas for over 20 min to replace N_2 in the alveoli. Venous mixture which still exists after inhalation of pure O_2 for a long time is the blood flow in the nonventilated alveoli In other words, it is the real venous shunt.

After the subject has breathed pure oxygen during cardiac catheterization, arterial blood is sampled from the indwelling needle in the brachial artery and is immediately centrifuged anaerobically under low temperature. The plasma O_2 tension is measured polarographically by a mercury electrode Oxygen tension in the alveoli is measured by the *Haldane-Priestley method*. The arteriovenous O_2 difference is determined from the blood gas analysis by the *Van Slyke manometric method*. The following equation may be obtained

$$\left\{ \begin{array}{l} \text{Anatomic venous} \\ \text{mixture ratio} \end{array} \right\} = 100 - \left(\frac{Y}{Y - G} \times 100 \right)$$

where Y = arteriovenous O_2 difference (vol %)
G = (alveolar PO_2 − arterial PO_2) × B
B = O_2 volume dissolved in blood under 1 mm Hg O_2 tension at 37.0°C (vol %)

CRITICISM OF THE METHOD At present, it is undoubtedly difficult to determine accurately the bronchial blood flow in man without surgery The above method involves a few difficulties (1) impossibility of a simultaneous measurement of pulmonary capillary blood flow and cardiac output in a steady condition, and (2) necessity of operator's skill and subject's cooperation for the CO_2 equilibration in the alveoli and for alveolar air sampling In the author's experiments, all measurements were always performed under the same basal conditions, evaluated through O_2 consumption and respiratory quotient, in order to maintain the patient's state as steady as possible The determination of alveolar air, after prolonged training of the subject, was repeatedly carried out in order to obtain constant values. Consequently, it

was found impossible to perform alveolar air sampling in patients with severe obstruction of the air passages (pulmonary emphysema, etc.), because of variability in the determination of alveolar air

The maximum error in determination of the cardiac output by the Fick's method should not be above 5 per cent, if the error in measurement of O_2 in the arterial and mixed venous bloods is only 0.1 vol per cent, when arteriovenous O_2 difference is 4 vol per cent. In the measurement of pulmonary capillary blood flow, on the other hand, an error of 0.5 mm Hg of alveolar CO_2 pressure corresponds to about 10 per cent of blood flow. Therefore, in the determination of the value of the bronchial blood flow, the above analytic error should be taken into consideration. After considering these points, however, it may still be concluded that in several patients with chronic pulmonary diseases, a large quantity of bronchial blood flows into the lungs

New Way of Measuring Bronchial Blood Flow by the Dye-dilution Method. At present, the dye-dilution method is employed in the author's laboratory for the measurement of bronchial blood flow. The method consists of a simultaneous measurement of left and right ventricular outputs with two cardiac catheters.

One catheter is introduced into an antecubital vein and advanced until the tip lies *in the main pulmonary artery*. Another catheter is advanced through a second vein until its tip lies *in the superior vena cava*. A Cournand needle is inserted into the bronchial artery. Three to four cubic centimeters of Evans blue or Bromsulphalein is rapidly injected into the superior vena cava. Simultaneously, blood is sampled *in small test tubes from* the pulmonary artery and brachial artery *every 1 to 2 sec*. In sampling from the pulmonary artery, the end of the catheter is inserted into a negative pressure chamber, with a pressure of about 200 mm Hg below atmospheric, and the small test tubes in the chamber are automatically rotated. Dye concentration in serum is measured by means of an electrophotometer, and two dye-dilution curves are inscribed

The curves drawn from the brachial artery and pulmonary artery should measure the outputs of the left and right ventricles, respectively. Then, the difference between the two should be attributed to an increase of the bronchial blood flow

Experiments were attempted at first in normal dogs, and the outputs of the left and right ventricles were found to be practically identical (Table 13-3). Then a shunt was made between the left subclavian and the left pulmonary artery in other dogs, and the outputs were measured by the dye-dilution method. At the same time, blood flow through the shunt was directly measured by means of a bubble flowmeter placed in the course of the shunt and by bleeding from the anastomotic

TABLE 13-3 COMPARISON OF LEFT AND RIGHT VENTRICULAR OUTPUTS BY THE DYE-DILUTION METHOD IN NORMAL DOGS

Dog No.	Body weight, kg	Ventricular output, L/min		Left − right, L/min
		Left	Right	
11	14.5	1.68	1.70	−0.02
12	11.5	2.26	2.50	−0.24
13	25.0	3.45	3.58	−0.13
14	11.0	2.31	2.15	+0.16
16	12.0	1.03	0.99	+0.04
19	10.5	1.26	1.26	0
20	16.2	1.21	1.22	−0.01
25	35.0	6.27	6.24	+0.03

TABLE 13-4 LEFT AND RIGHT VENTRICULAR OUTPUTS BY THE DYE-DILUTION METHOD AND SHUNTED BLOOD FLOW IN DOGS WITH LEFT SUBCLAVIAN-PULMONARY ARTERIAL ANASTOMOSIS

Dog No	Body weight, kg	Ventricular output, L/min		Left − right, ml/min	Bubble flowmeter method, ml/min	Bleeding method, ml/min
		Left	Right			
16	12.0	1.95	1.83	120	110	185
17	15.0	2.63	2.26	370	480	500
19	10.5	1.40	0.99	410	480	500
25	35.0	5.46	5.05	410	480	340

Table 13-5. Comparison of Left and Right Ventricular Outputs by the Dye-dilution Method in Healthy Persons

Subject	Ventricular output, L/min		Left − right, L/min	$\frac{\text{Left} - \text{right}}{\text{Right}} \times 100$ (%)
	Left	Right		
G S	6 82	7.29	−0.47	−6.4
F T.	6 58	6.80	−0.22	−3.2
Y.A.	6 87	6 81	+0.06	+0.9
A S *	10 39	10 38	+0.01	+0.1
	10 02	9.79	+0.23	+2.3
Y.T	5 53	5 46	+0.07	+1.3
	5 70	5 61	+0.09	+1.6
S Y	8.15	8.71	−0.56	−6.4
T K.	6 55	6.13	+0.42	+6 9
H.T.	6 30	6 27	+0.03	+0.5

* This person was not in a basal condition

Table 13-6 Left and Right Ventricular Outputs and Bronchial Blood Flow by Dye-dilution Method in Patients with Chronic Pulmonary Diseases

Patient	Diagnosis	Ventricular output, L/min		Bronchial blood flow (BBF), L/min	$\frac{\text{BBF}}{\text{Right cardiac output}} \times 100$ (%)
		Left	Right		
J O.	Silicosis (grade I) Tuberculosis (minimal)	4 20	4 14	0 06	1 4
T Y	Silicosis (grade I) Tuberculosis (minimal)	6 72	6 39	0 33	5 1
M T	Silicosis (grade I)	8 70	8 94	−0 24	−2 6
T T	[illegible]	4 22	4 33	−0 11	−2 5
C F		3 97	4 09	−0 12	−2 9
M Y		6 43	6 08	0 35	5 7
C Y		7 71	6 85	0 86	12 5
T K		6 88	6 01	0 87	14 4
M K.		7 78	5 00	2 78	55 6
S H		4 29	2 97	1 32	44 6
S Y.	Silicosis (grade III) Tuberculosis (far-advanced)	8 55	7 67	0 88	11 4
T T	Emphysema	5 41	4 92	0 49	10 0
K I.	Bronchiectasis	6 59	5 92	0 67	10.9
H S	Bronchiectasis	9 31	7 56	1 75	23 1
R Y	Pulmonary tuberculosis	5 88	5 72	0 16	2 8
K S	Pulmonary tuberculosis (moderately advanced)	8 19	5 60	2 59	46.3
K S.	Bronchial cancer	6 30	5 97	0 33	5 5
C.T	Metastatic lung cancer	10 15	7 79	2 36	30 3

Table 13-7 Bronchial Blood Flow in Three Healthy Persons

Subject	Incoming CO_2		Outgoing CO_2		CO_2 output, ml/min	Pulmonary capillary flow, L/min	Right cardiac output, L/min	Anatomic venous admixture ratio, %	Bronchial blood flow, L/min
	Alveoli, %	Blood, vol %	Alveoli, %	Blood, vol %					
M.C	7.38	65 5	6 52	61.7	264	7.00	7 08	1 0	−0.01
T.U.	6.32	51.5	5.50	47.6	209	5.46	5 80	1 9	0 11
U T.	7.33	58.9	6.52	55 8	180	5 87	5.58	1 2	0.36

channel Table 13-4 shows that the difference between the two outputs corresponded roughly to the values obtained by the flowmeter and bleeding method Examination of these results led to the conclusion that the method was sufficiently accurate for measuring the shunted blood flow.

The difference between the outputs of left and right ventricles in healthy persons corresponded within 10 per cent of the right cardiac output in all (Table 13-5). However, in patients with tuberculosilicosis, bronchiectasis, pulmonary tuberculosis, or cancer of the lung, it was frequently observed that the difference was much greater (Table 13-6). It reached 53 per cent of the right cardiac output in a patient suffering from silicosis with massive density, while no such difference was noted in simple silicosis or in early stages of this condition plus minimal tuberculosis These figures agree fairly well with the results obtained by previously mentioned methods.

BRONCHIAL BLOOD FLOW IN HEALTHY PERSONS

According to the determinations of blood-flow studies in three healthy persons, pulmonary capillary blood flow presented a value close to cardiac output (Table 13-7). Bronchial blood flow was calculated to be 0 01 to 0 36 liters/min Considering the errors which must accompany this measurement, this is unquestionably insignificant The above results obtained from healthy persons are important for comparison with results obtained in diseased lungs

BRONCHIAL VASCULAR SYSTEM AND BLOOD FLOW IN CHRONIC PULMONARY DISEASES

In certain *chronic pulmonary diseases*, the increase in bronchial circulation has been well established by Liebow (1949, 1950) and others. The author's morphologic studies proved indirectly a similar phenomenon. In these conditions, when the bronchial blood flow was measured physiologically, an abnormally large figure was frequently obtained In cases with *destruction of pulmonary artery branches in diseased areas* (pulmonary tuberculosis, bronchiectasis, pulmonary silicosis), the bronchial artery was found to be remarkably developed Its dilated, twisting branches could be observed by the naked eye (Fig



Fig 13-15. A Marked twining and dilatations of the bronchial artery at the hilar region. Adult lung affected by tuberculosis (vinyl plastic cast) A p, pulmonary artery; A. br., bronchial artery B. Enormous plexiform branches of the bronchial artery form a fine mesh and wrap the tuberculous cavity from the hilus side, while nearly all the branches of the pulmonary artery are damaged around the cavity. Br, bronchus, A br, bronchial artery; P., enormous plexiform branches of bronchial artery; C, cavity. C. Bronchial arteries wind with marked development, while the pulmonary arteries are destroyed on the dilated bronchi and removed. Idiopathic bronchiectasis. Vinyl plastic cast Br, bronchus, A p, pulmonary artery; A br, bronchial artery.



Fig. 13-16. A Anastomosis between the bronchial artery and pulmonary artery in the neighborhood of the affected area. Idiopathic bronchiectasis Vinyl plastic cast. A., anastomosis; A p., pulmonary artery; A.br., bronchial artery. B Dilatation and development of the bronchial arteries in the vicinity of conglomerated nodules. Marked inflammatory changes are present on the bronchial wall. Silicotic lung

13-15). Moreover, in the neighborhood of the affected areas, the anastomoses between the bronchial and pulmonary arteries are developed in a high degree (Fig 13-16) It may be noticed that *the bronchial artery is so dilated that it reaches the caliber of the pulmonary artery with which it anastomoses.* When such lungs are irrigated by saline solution through the bronchial artery at the autopsy table, the solution will flow out easier from the pulmonary artery than from the pulmonary vein, which is the normal passage (Fig. 13-16B)

The values of bronchial blood flow in six cases of *bronchiectasis* are presented in Table 13-8. When these results are compared with those of healthy persons or with data of cardiac output, attention should be paid to very high figures (last column).

The data obtained in cases of *silicosis* showed the same trend (Table 13-9). Ten of 13 examined cases, however, also had *tuberculosis,* which may contribute to the increase of bronchial blood flow. Wood and Miller, and Wells, described the overdevelopment of the bronchial arteries in silicosis According to the author's histologic studies in cases with simple *silicosis,* the dilatation and overdevelopment of the bronchial artery cannot always be demonstrated around pure silicotic nodules If, however, *bronchitis* or *any other inflammatory condition* is associated with the process, overvascularization is usually encountered (Fig. 13-16B).

Of three cases of uncomplicated silicosis which the author studied, the bronchial blood flow in two showed an increase to 0 26 and 0.61 liters/min, respectively, whereas, in the other case, a remarkable increase up to 3 55 liters/min was obtained Such an increased flow may be due to the afore-mentioned reasons

Table 13-8 Bronchial Blood Flow in Six Cases of Bronchiectasis

Subject	Incoming CO_2		Outgoing CO_2		CO_2 output, ml/min	Pulmonary capillary flow, L/min	Right cardiac output, L/min	Anatomic venous admixture ratio, %	Bronchial blood flow, L/min
	Alveoli, %	Blood, vol %	Alveoli, %	Blood, vol %					
I.A	6.86	64.1	6 00	60.1	207	5.23	5 81	9.3	−0.07
S K	6.94	60.1	5.82	55 1	246	4 89	5 46	6.1	−0 25
E C	6.35	46.5	5 75	44.0	201	8 07	7.70	4 5	0.75
S H	6.46	48.7	5.61	46 1	171	6 36	5 65	9.4	1.37
T.A.	7.07	62.3	6.23	58.7	290	8 30	7 65	8 5	1.38
G.T.	7.22	60.1	6.20	55 6	218	4 90	3 52	7.5	1.78

TABLE 13-9. BRONCHIAL BLOOD FLOW IN 13 CASES OF SILICOSIS

Subject	Incoming CO_2		Outgoing CO_2		CO_2 output, ml/min	Pulmonary capillary flow, L/min	Right cardiac output, L/min	Anatomic venous admixture ratio, %	Bronchial blood flow, L/min
	Alveoli, %	Blood, vol %	Alveoli, %	Blood, vol %					
M S	6.94	47.5	6.15	44.4	154	4.07	3.76	1.8	1.30
Ky S	7.27	55.8	6.29	52.8	221	7.53	5.76	(3.3) †	2 03
T S *	7 17	60 0	6.15	56.1	160	4.15	4.20	6.9	0.26
T Y.*	7.18	51.0	6 51	47.7	195	6.01	5.60	3.3	0.61
S S	6 81	48 2	6 02	45.1	208	6.86	5.81	3.9	1.33
R H	6 37	49 7	5.45	46.8	193	6.69	4.51	1.2	2.23
Ku.S *	6 40	53.0	5.89	50 5	172	6.82	3 62	5.0	3.65
H S	7 15	61 8	6.28	57 9	210	5.45	4.52	0.3	1.49
Z T	6 42	49.7	5.82	46.3	178	5.23	3.61	(3.3)	1.80
Z I	5 37	45 4	4.90	42.1	206	6 85	5.86	(3.3)	1.22
S Y	7 16	59 1	6 23	54.4	241	5.01	3.36	(3.3)	1 86
H Y	7.13	58 8	6 35	55 6	199	6.26	5.50	1.1	0.83
Ki S.	5 95	48 1	5 45	45.5	191	7.13	6.61	(3 3)	1.08

* Simple silicosis

† Unmeasured value. Averaged value in 8 cases of silicosis.

It is surprising that the bronchial blood flow increases to such an extent in these diseases.[a] According to the author's method, the measured value represents only the blood flow which reaches the pulmonary capillaries by way of the anastomosis between arterial systems This does not include the bronchial blood flow which returns immediately into the pulmonary veins Systemic blood flow from the intercostal arteries via pleural adhesions is also presumed to be of a large order

COR PULMONALE SECONDARY TO CHRONIC LUNG DISEASES

The incidence of cor pulmonale in chronic lung diseases has been reported by many investigators Using the criteria of Scott et al and Griggs et al, the author measured the walls of the left and right ventricle in 99 persons with healthy or diseased lungs (Table 13-10). The results were similar to those of others. Right ventricular hypertrophy (wall of right ventricle over 5 mm) was found in persons with pulmonary emphysema, silicosis, bronchiectasis, and pulmonary tuberculosis. *In most of these persons, the left ventricle was also found to be hypertrophied.*

In cor pulmonale, left ventricular hypertrophy has been reported by others Spain and Handler examined cases without systemic hypertension, aortic valvular diseases, or coronary arterial changes, and *found left ventricular hypertrophy in 90 per cent of the cases* The author's studies proved that the wall of the left ventricle measured over 12 mm in 61 per cent of the cases Even though several mechanisms (systemic hypertension, hypoxia, increase of cardiac output, anatomic connection between the muscle fibers of the left and right ventricles, and myocardial damage) were suggested, the explanations are mostly not satisfactory.

Cor pulmonale is a common occurrence in bronchiectasis, silicosis, and pulmonary tuberculosis. In the same conditions the bronchial arterial system is remarkably overdeveloped and the bronchial blood flow is conspicuously increased. This blood flow from the left

[a] In these affected lungs, simultaneous measurement of the bronchial blood flow and the pulmonary blood flow has been attempted [illegible]

[illegible] venous admixture, [illegible] physiologic [illegible] monary blood flow is classified and its significance is studied (Table 13-9) The results shown are from one of the cases with silicotuberculosis

TABLE 13-10. THICKNESS OF CARDIAC WALL IN 99 PERSONS WITH HEALTHY OR DISEASED LUNGS

	No. of persons	*Weight of heart, Gm*				*Thickness of cardiac wall, mm*				
		<200	201-300	301-400	>401	*R.V.**		*L.V.*†		*R.V.* >5.1 *L.V.* >12.1
						<5.0	>5.1	<12.0	>12.1	
Normal person	17	4	9	4		17		16	1	
Emphysema	9		4	5		4	5	4	5	3
Asthma	1			1			1		1	1
Bronchiectasis	9	1	4	3	1	6	3	5	4	2
Gangrene	2			2		1	1	2		
Simple silicosis	10	2	4	4		6	4	9	1	1
Silicosis + tuberculosis	9	1	6	2		3	6	4	5	4
Silicosis + cancer	2		2				2		2	2
Tuberculosis	6	1	4		1	5	1	5	1	1
Miliary tuberculosis	2		2			2		2		
Primary lung cancer	11	2	9			11		9	2	
Metastatic lung cancer	13		9	4		13		12	1	
Miscellaneous	8		5	3		8		8		
Total	99	11	58	28	2	76	23	76	23	14

* R.V., right ventricle
† L.V., left ventricle

ventricle enters the lung via branches of the aorta and returns to the left ventricle via the pulmonary veins. In the discussion of the cardiopulmonary dynamics in such diseases, the bronchial blood flow plays an important role The left and right cardiac outputs of patients with pulmonary diseases should be carefully determined, with proper consideration of the special nature of the bronchopulmonary circulation.

CRITICAL ANALYSIS OF THE LEFT AND RIGHT CARDIAC OUTPUTS

When there is no shunt or abnormality in pulmonary blood flow, the cardiac outputs from the two ventricles are considered to be equal Cardiac output is calculated by Fick's principle according to the following equation:

$$\text{Cardiac output} = \frac{O_2 \text{ intake}}{\left\{\begin{matrix}\text{arterial } O_2 \text{ content} \\ - \text{ mixed venous} \\ O_2 \text{ content}\end{matrix}\right\}} \qquad (1)$$

Strictly speaking, in normal lungs, the left and the right cardiac outputs are different because of the existence of bronchial arteries and thebesian vessels. However, this theoretic difference is minimal and is within the margin of error of cardiac output measured by cardiac catheterization. Therefore, in the normal lung, the left and right cardiac outputs are considered practically equal

In the above-mentioned diseases, the bronchial blood flow which returns to the left atrium occasionally amounts to over 2 liters (over 30 per cent of cardiac output). Consequently, cardiac outputs from the left and right ventricles will be different. The left cardiac output in Eq. (1), based on Fick's principle, does not include the bronchial blood flow which supplies blood to the lung and returns to the pulmonary veins, bypassing the right atrium The right and left cardiac outputs should, therefore, be corrected in the following way

Right cardiac output = (cardiac output based on Fick's principle) − (bronchial blood flow which drains into pulmonary veins and blood flow of the thebesian vessels)

Left cardiac output = (cardiac output based on Fick's principle) + (bronchial blood flow)

The right cardiac output based on Fick's principle will actually show a value less than that which includes the blood flow of the bronchial and thebesian vessels The blood flow of the bronchial and thebesian vessels cannot be measured at present However, its value is negligible

The results of the left and right cardiac outputs measured in cases with *silicosis* and *bronchiectasis* are shown in Tables 13-11 and 13-12. When the right cardiac output is presumed to be 100, the left cardiac output will be 106 to 198 (average 131). Obviously, the right and left cardiac out-

This finding can be verified by the following experiment. When the pulmonary artery of a dog is ligated, the bronchial arteries will develop considerably. Using the bubble flowmeter technique, the bronchial arterial blood flow was directly measured in a dog with ligation of the pulmonary artery for 5 months, it showed 17.8 ml/min, or 14.2 times as high as that of a normal dog. Using the bronchospirometric method of Bloomer et al., the effective bronchial blood flow, after a lapse of time, was found to be increased in dogs with preligated pulmonary artery. The left and right cardiac outputs were found to be remarkably different within 5 to 8 months (Table 13-13).

In another experiment on *pulmonary embolism*, the bronchial blood flow was found to be not increased at the beginning of the episode, but it increased gradually to 50 ml/min after 3 months. Clinically, this was confirmed in a case with pulmonary embolism

In *chronic lung diseases*, a large amount of blood flow from the bronchial artery will drain into the lung, which will increase blood return to the left atrium Consequently, *the left ventricle has to expel more blood than the right.* Such strain will eventually cause left ventricular hypertrophy.

The development of the bronchial vascular

TABLE 13-11 RIGHT AND LEFT CARDIAC OUTPUTS IN 13 CASES OF SILICOSIS

Subject	*Right cardiac output, L/min*	*Bronchial blood flow, L/min*	*Left cardiac output, L/min*	*Right left*
T S	4 20	0 26	4 46	100 106
T Y	5 60	0 61	6 21	100 111
H Y	5 50	0 83	6 33	100 115
Ki S	6 61	1 08	7 69	100 116
Z L	5 86	1 22	7 08	100 121
S S	5 81	1 28	7 09	100 122
H S	4 52	1 49	6 01	100 133
M S	3 76	1 30	5 06	100 134
Ky S	5 76	2 03	7 79	100 135
R H	4 54	2 23	6 77	100 149
Z T.	3 61	1 80	5 41	100 150
S Y	3 36	1 86	5 22	100 155
Ku S	3 62	3 55	7 17	100 198
Average	4 83	1 50	6 33	100 131

TABLE 13-12 RIGHT AND LEFT CARDIAC OUTPUTS IN SIX CASES OF BRONCHIECTASIS

Subject	*Right cardiac output, L/min*	*Bronchial blood flow, L/min*	*Left cardiac output L/min*	*Right left*
I A	5 81	0	5 81	100 100
S K	5 40	0	5 40	100 100
I C	7.70	0 75	8 45	100 110
S H	7 65	1 38	9 03	100 118
T A	5 65	1.37	7.02	100 124
G T.	3 52	1.78	5 30	100 151
Average	5.04	0 88	6 84	100 115

system and the increase of left ventricular output unquestionably play an important role in determining left ventricular hypertrophy. On the other hand, the influence of the blood pressure of the bronchial artery upon the pulmonary circulation, in parallel with the development of anastomosis between the two arterial systems has been pointed out as a contributory factor in causing right ventricular hypertrophy. It can be easily understood that the development of the bronchial vascular system in chronic pulmonary diseases is actually placing an additional burden upon both ventricles.

In the discussion of cor pulmonale in chronic pulmonary diseases, pulmonary emphysema was omitted. This condition will be the object of a subsequent study.

TABLE 13-13 RIGHT AND LEFT CARDIAC OUTPUTS IN DOGS WITH LEFT LIGATED PULMONARY ARTERY

Dog No	*Days after ligation*	*Right cardiac output L/min*	*Effective bronchial arterial flow, L/min*	*Left cardiac output L/min*	*Right left*
15	163	3 39	0 63	4 03	100 118
13	180	3 34	0 85	4.19	100 125
22	200	3 33	0 89	4 22	100 126
6	253	2 95	0 47	3 43	100 116

4

Right heart catheterization in chronic cor pulmonale

T. K. LIN

In order to understand the pulmonary hemodynamic changes that occur in chronic cor pulmonale, the dual pulmonary blood supplies of the pulmonary and bronchial arteries should be studied first.

Each bronchial artery courses along the posterior wall of its bronchus and enters the hilum of the lung. Its branches supply arterial blood to the bronchi, bronchioles, tracheobronchial and interbronchial lymph nodes, and the vasa vasorum of the pulmonary arteries

The common venous return for these two arterial systems of the lungs is by way of the pulmonary veins. However, the blood supply to the pleura, hilar, and mediastinal structures can be divided into the following three groups:

1. The visceral pleura is supplied by the visceral branches of both the pulmonary and bronchial arteries. The pulmonary veins provide venous drainage for these capillaries.

2 The hilar structures and the first- and second-order bronchi are supplied by the bronchial arteries The true bronchial veins are their venous drainage.

3. The extrapulmonary vessels, such as those of mediastinal structures, are supplied by the bronchial and mediastinal arteries. The azygos vein and its branches serve as venous drainage for these capillaries. Ultimately, the drainage of both the second and third groups is via the azygos system into the right atrium

Under normal conditions, the following anastomoses have been demonstrated. (1) capillary and arteriolar anastomoses between bronchial and pulmonary arteries, (2) anastomoses between pulmonary arteries and veins; (3) anastomoses between bronchial and pulmonary veins.

Figure 13-17 indicates the pulmonary and bronchial circulations. The dotted line represents the anastomoses present in normal lungs In normal dog lungs, about 99 per cent of the pulmonary blood supply is derived from the pulmonary arteries and 1 per cent from the bronchial arteries. Therefore, the left ventricular output is approximately 1 per cent greater than the right ventricular output. The blood flow through these anastomoses and the bronchial circulation is usually negligible under normal conditions However, in chronic pulmonary disease and in certain congenital heart diseases with inadequate pulmonary arterial blood supply (such as severe pulmonary stenosis or Fallot's tetralogy), the collateral bronchial arterial and bronchopulmonary venous systems become very extensive. Large anastomoses from these preexisting areas are greatly augmented Different types of shunts may develop. The type of shunt, degree of polycythemia, hypervolemia, presence of pulmonary hypertension, or possibly the competency of the azygos venous system, determine the extra work load upon the ventricles

Under normal resting conditions, the pulmonary arterial pressure is 25/10 mm Hg, with a mean pressure of 13 to 15 mm Hg. The mean pulmonary artery wedge pressure ranges from 3 to 12 mm Hg, depending upon whether the cardiac catheter tip is wedged posteriorly or anteriorly in a supine position.

Under moderate exercise, oxygen consumption may increase to 300 to 912 ml/min with a twofold increase of arteriovenous oxygen difference and threefold increase of cardiac output. However, the pulmonary arterial pressure

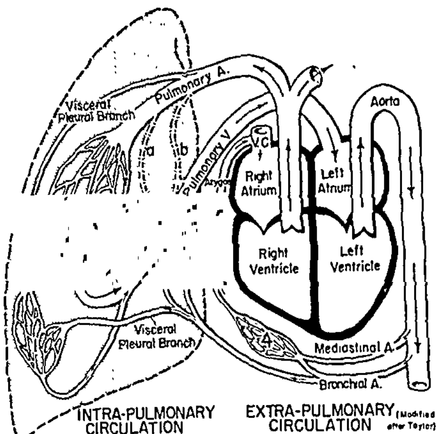


Fig. 13-17. Diagram indicating the pulmonary and bronchial circulations

shows no significant rise. Patients undergoing pneumonectomy show an average increase of 40 per cent in the systolic pulmonary pressure at the time of ligation of the pulmonary artery. The remaining pulmonary vascular bed, however, compensates for the added load in about 30 to 90 min Postpneumonectomy patients can accommodate a two- or threefold increment in the pulmonary blood flow with only a minimal increase in the pulmonary artery pressure, provided the remaining lung is normal Table 13-14 indicates the different hemodynamic changes between normal individuals and patients with chronic cor pulmonale.

In addition to the above-mentioned conditions, acute digitalization may produce a fall in the pulmonary arterial pressure in patients with chronic cor pulmonale associated with predominant left ventricular failure. The respiratory variations in pulmonary artery blood

TABLE 13-14 HEMODYNAMIC CHANGES IN CHRONIC COR PULMONALE

	Pressure, mm Hg				Cardiac index, L/min/M2	Arterial O_2 saturation, %	Blood pH
	RA	RV	PA	PAW			
Normal person	(0–5)	25/0–2	25/10 (15)	(5–12)	2 2–4 5	96	7.43
Chronic cor pulmonale							
1 Resting	N or ↑	N or ↑	N or ↑	N	N or ↑ or ↓	N or ↓	N or ↓
2 Digitalization							
a Without right heart failure	No appreciable changes						
b With right heart failure	↓	Increased systolic, decreased diastolic pressure	↑	N	↑	N or ↑	

RA, right atrium, RV, right ventricle, PA, pulmonary artery, PAW, pulmonary artery wedge; N, normal; ↑, increased, ↓, decreased.

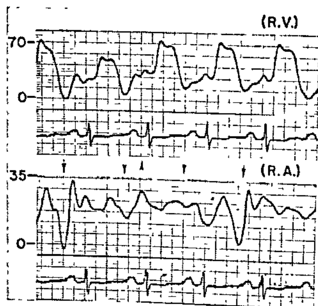


Fig. 13-18. Right heart pressure patterns simulating constrictive pericarditis but due to advanced chronic cor pulmonale.

pressure are marked in chronic cor pulmonale

The right heart pressure pattern in chronic cor pulmonale is best classified into that of right ventricular hypertrophy with or without right ventricular failure As far as the *work load* of the right ventricle is concerned, it can be due to increase of pulmonary pressure or pulmonary flow, or both When there is an increase of pulmonary flow secondary to an increase of the circulating blood volume, there is *an increase of right ventricular work, but the pulmonary pressure may not be elevated* In more advanced cases, both pulmonary hypertension and hypervolemia are usually present. The increase of blood viscosity due to secondary polycythemia may also contribute some extra work load to the right ventricle In the late stage of chronic cor pulmonale with ventricular failure, there is *a rise of right ventricular end diastolic pressure to 7 to 10 mm Hg or more,* owing to marked increase of right ventricular residual blood volume and inadequate emptying. An accompanying *functional tricuspid insufficiency* may also develop. However, *the pulmonary artery wedge pressure remains normal* throughout these stages

Various pathologic conditions which hinder effective ventricular contraction or diastolic relaxation will produce a similar right ventricular pulse pressure pattern. These conditions are constrictive pericarditis, pericardial tamponade, myocardial fibrosis, amyloidosis of the heart, other infiltrative process of the ventricle, subendocardial fibroelastosis, and right ventricular failure (other than that of chronic cor pulmonale). These conditions usually have a biventricular involvement, and the pulmonary artery wedge pressure is often elevated Figure 13-18 shows right ventricular and atrial pressure patterns simulating those of constrictive pericarditis but due to advanced chronic cor pulmonale.

In the presence of right ventricular hypertrophy, only a slight increase of the right atrial pressure occurs. The presence of a giant A wave may be explained on the basis of lesser distensibility of the hypertrophied right ventricle. The mean right atrial pressure will increase further as the right ventricle starts to fail. In the advanced stage, the increase of mean right atrial pressure can be due to (1) right ventricular hypertrophy, (2) right ventricular failure producing a high right ventricular end-diastolic pressure, or (3) functional tricuspid regurgitation.

In the early stage of chronic cor pulmonale, a mild degree of pulmonary hypertension may be present. In the late stage, a marked pulmonary hypertension usually ensues, with a compensating prolongation of the pulmonary systolic ejection phase. As the disease approaches the end of its course, the gradient between the right ventricular end-diastolic and pulmonary diastolic pressures becomes less and less.

The cardiac output in patients with chronic cor pulmonale depends on several factors.

1 Degree of pulmonary arterial resistance Some patients fail to increase cardiac output because of marked increase of pulmonary resistance These patients have a high pulmonary artery pressure.

2 Right ventricular reserve A failing right ventricle may not be able to increase the cardiac output

3 Increased circulating blood volume due to secondary polycythemia Usually, there is an increase in cardiac output if the right ventricular reserve is in good condition and there is no significant degree of pulmonary hypertension

4 Other complicating conditions, such as the status of the left heart, and other associated lesions

A few disease entities producing chronic cor pulmonale are briefly discussed below.

Chronic pulmonary emphysema has been most intensively studied. The majority of patients with a severe degree of pulmonary emphysema exhibit some degree of pulmonary hypertension The correlation between increase in pulmonary arterial pressure and the ratio of the residual lung volume to total lung volume is only moderate Cardiac index correlates inversely with the severity of pulmonary hypertension Evidence indicates that hypoxia plays a definite role in the production of the pulmonary hypertension. In most instances, administration of O_2 to patients with hypoxia and pulmonary hypertension will reduce the pulmonary arterial pressure. Cardiac output could be normal, decreased, or increased

Recently, the author has studied 10 cases of *preoperative and postoperative excision of emphysematous bullae* A transitory decline of pulmonary hypertension following bullectomy in the severe cases, with pulmonary insufficiency, hypoxia, and right heart failure, is striking However, there is a tendency to the progressive return to their preoperative level as the underlying chronic pulmonary emphysematous process proceeds Pulmonary function studies are not altered by the surgical excision

Liebow et al. (1949, 1950) have demonstrated a definite *left-to-right shunt from the bronchial arteries to the pulmonary arteries* in chronic bronchiectasis by obtaining a highly oxygenated blood sample in the pulmonary artery. This shunt will increase the left ventricular work, provided the pulmonary arterial pressure remains normal

The characteristic changes in *pulmonary capillary alveolar block* are the following Reduction of lung volume, maintenance of a large maximum breathing capacity, hyperventilation at rest and during exercise, nearly normal resting arterial O_2 saturation, marked arterial O_2 desaturation after exercise, normal alveolar O_2 tension, reduced O_2 diffusion, and pulmonary hypertension. Carbon dioxide *is* twenty-five times more diffusible than O_2 Therefore, a significant CO_2 diffusion barrier cannot exist without a fatal block to O_2 transfer. Carbon dioxide retention and *respiratory* acidosis are frequent clinical entities but always result from ventilatory or distributional *abnormalities* and not from pure diffusion difficulties.

Recurrent pulmonary embolism will produce a clinical picture of cor pulmonale. As the disease progresses, marked pulmonary hypertension associated with decrease in cardiac output, systemic peripheral vascular constriction, increased arteriovenous O_2 difference, and peripheral blotching will occur. Cardiac arrhythmias may be the terminal event. Primary pulmonary hypertension may give a similar picture, as in some cases of chronic recurrent pulmonary embolism

Polycythemia of obesity is a type of chronic cor pulmonale which is due to pulmonary alveolar hypoventilation, secondary to massive obesity This condition is characterized by arterial hypoxia and CO_2 retention, causing a variable degree of cyanosis and heart failure. The pulmonary arterial pressure varies from a slight to a moderate elevation, with normal pulmonary artery wedge *pressure, and an increase* of blood volume mainly due to increase *of red cell mass* A marked variation of peripheral arterial O_2 saturation is correlated with respiratory change. A fall arterial O_2 saturation can be achieved after inhalation of 100 *per cent* O_2. *These* abnormal changes will reverse to normal after a satisfactory weight reduction.

Different pharmacologic agents alter the pulmonary hypertension Administration of aminophylline, Priscoline, hexamethonium, *tetraethyl*ammonium bromide, sodium nitrate, dibenamine, or inhalation of 100 per cent O_2 will somewhat reduce pulmonary hypertension. In normal individuals, the infusion of *acetylcholine* into the main pulmonary artery at a rate of 0.5 mg/min causes a slight or *questionable* fall in pulmonary artery pressure. However, if pulmonary hypertension is due to hypoxia, the fall in pressure due to acetylcholine is very significant There is no change in either pulmonary *artery* wedge pressure or cardiac output. The administration of dihydroergotamine or acute anoxia will increase the pulmonary arterial pressure Intravenous injection of epinephrine gives rise to a transitory elevation of pulmonary arterial pressure. Papaverine, *given by* the intravenous route, causes no appreciable changes in the pulmonary arterial pressure In other words, an ideal satisfactory pulmonary antihypertensive agent has not yet been discovered

5

Roentgenology of cor pulmonale

FELIX G. FLEISCHNER

ACUTE COR PULMONALE

While the concept of chronic cor pulmonale goes back to observations by pathologists of hypertrophy and dilatation of the right ventricle in the presence of chronic pulmonary disease, the idea of acute cor pulmonale, a transient functional condition, was conceived by clinicians (McGinn and White, 1935). It is based on the concept of acute pulmonary hypertension and its reflection upon the heart. Acute cor pulmonale has been connected almost exclusively with pulmonary embolism. However, an analogous cardiovascular condition had been observed in rare cases with severe exacerbation of bronchial asthma (Turiaf et al).

A single episode of pulmonary embolism without infarct formation, if not fatal, often does not leave permanent gross morphologic changes. Roentgenologically, accordingly, the condition of acute cor pulmonale is usually believed not to be recognizable There are, however, a few roentgen observations which belong to this entity. Westermark (1938) has described a lack of blood filling of the lung of lobar or segmental extent causing increased translucency, more recently called *oligemic lung*. This observation has been confirmed by others. Why this sign is not manifest more commonly or could not be confirmed in the experimental animal is not understood, but this does not invalidate its correctness and value, when present.

The *plump, tumor-like hilar shadow* is another possible sign. Hanelin and Eyler have analyzed cases of massive chronic and subacute pulmonary embolism with large embolothrombi lodged in the hilar arteries. They convincingly demonstrated that these large thrombotic masses may form the core of the plump hilar shadows. Thus, pulmonary artery obstruction may play a direct important part in the syndrome of acute cor pulmonale and in the causation of the roentgen signs of oligemia of the lung fields and plump hilar shadows However, clinicopathologic correlation suggests that functional phenomena involving the pulmonary vasculature, i.e., reflexes originating from arteries lodging emboli, play a role, too. These phenomena, corresponding to Wood's vasoconstrictive and reactive pulmonary hypertension, and their roentgen signs do not permit of close roentgenpathomorphologic correlation. In a similar fashion, the acute cor pulmonale syndrome may lack a morphologic counterpart on the necropsy table This presentation follows the well-founded assumption that the embolic insult triggers reflexes in the cardiopulmonary system, involving the pulmonary vasculature (P. Wood, 1952), respiratory center, bronchi, diaphragm, etc In the endeavor to recognize pulmonary embolism, even though there may not be gross infarct formation, one learns to rely on functional roentgen signs. It is assumed that the embolic insult incites spastic contraction of medium-sized and small pulmonary arteries and arterioles This arteriospasm, acting in addition to the mechanical block, causes the extraordinary increase in pulmonary resistance and the extra load on the right ventricle.

Examination. The old clinical experience, that a patient recovering from an operation

may be seized by a fatal embolism while rising for the first time, prompts the question whether a roentgen examination for pulmonary embolism is advisable at all To answer this question one has to classify the patients into two groups, those in whom the diagnosis of embolism has not yet been made, and those in whom it has been made. The first group includes patients sent for a roentgen examination with no diagnosis or with a tentative diagnosis of upper respiratory infection, viral pneumonia, pleurisy, endemic pleurodynia, angina pectoris, convalescence from myocardial infarct, cholecystitis, left epigastric pain, etc. These patients may walk to the examination room or arrive in a wheel chair or on a stretcher because the attending physician expects important information. If on immediate inspection of the film, anything points in the direction of embolism with or without infarct, one should continue the examination by further questioning the patient, and using fluoroscopy with *spot films*, or using special standard views Thus, one may occasionally arrive at a diagnosis of pulmonary embolism at once or, more often, find suggestive hints which may lead to the clinical diagnosis later on.

In patients in whom the diagnosis of pulmonary embolism has been made on clinical grounds, anticoagulant treatment, vein ligation, or both have been started immediately Most physicians, however, are interested in a subsequent confirmation of the diagnosis and in a follow-up observation. The anticoagulant medication seems to provide sufficient protection; in several hundred such examinations, no untoward complication has occurred in the hospital in which the author works The examinations are carried out after several days of treatment with the patient sitting in his bed, on a stretcher or a stool, or standing according to the regimen prescribed by his physician and the condition of the patient.

The clinically postulated acute dilatation of the right ventricle can only rarely be recognized by the roentgenologist The pulmonary artery trunk, forming the second curve on the left in the posteroanterior view, may show a slight, seldom a marked bulge In most instances of first-episode embolism, it is difficult to recognize this bulge because there exists a wide range in the normal appearance of the second arch on the left However, during a close follow-up or if a previous roentgenogram is available for comparison, a definite trend to dilatation of the pulmonary artery can be recognized. *This is most marked between the second and the tenth days* and may subside in the following weeks. A decrease in width may permit the diagnosis of transient hypertension, i.e., acute cor pulmonale, in retrospect.

The hilar shadows are almost entirely made up of the branches of the pulmonary artery. Only the upper lobar veins cross them in somewhat confusing fashion. The right hilar arteries, and particularly those forming the lower half of the hilar shadow, present themselves best, owing to the anatomic arrangement, in a more coronal plane of the branches of the right pulmonary artery. The left branches are oriented in a more sagittal plane and are partially obscurred by the cardiovascular shadow. Thus, the lower two-thirds of the right hilar shadow presents the widths of the pulmonary artery branches in measurable fashion standing out against the air channel of the intermediary bronchus. The *absolute width* of this arterial band shadow varies individually but is fairly constant in the same subject. Increased width and convexity of the lateral contour are reliable signs of pulmonary arterial hypertension, and this change can even be quantitated to a certain degree.

The stress placed upon the right ventricle causes difficulties to the venous return Increased right ventricular pressure in itself interferes with passive filling of the ventricle and causes stagnation in the right atrium. Engorgement of the right atrium is further accentuated when decompensation sets in with increased diastolic pressure of the right ventricle, and becomes maximal if there is relative tricuspid insufficiency. This engorgement, clinically recognized by dilatation and pulsation of the neck veins and by the elevated venous pressure, is often clearly depicted on the roentgenogram by dilatation of the azygos vein and superior vena cava.

An Illustrative Case. A young man of 28 years was admitted to the hospital on June 8, 1955, with stabbing chest pain on the right, and a small amount of hemoptysis On June 15, the diagnosis of pulmonary embolism with infarct was established and heparin treatment started. The first set of roentgenograms shows the right hilar . . .

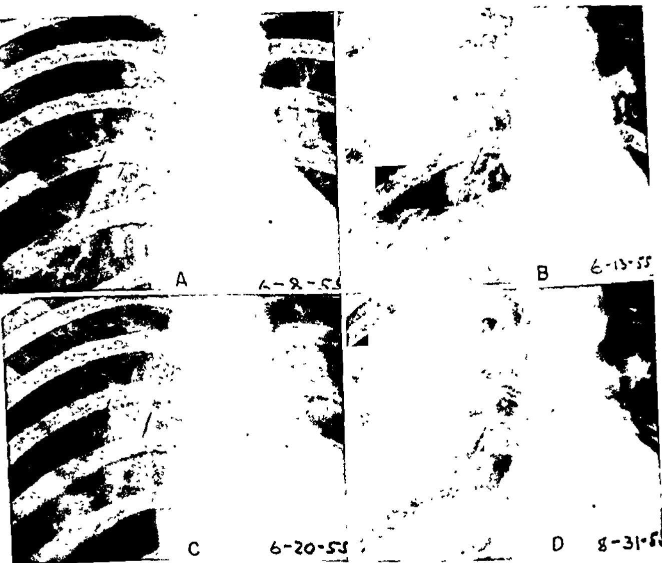


Fig. 13-19. Episode of pulmonary embolism with roentgen signs of acute cor pulmonale See text

on the day of admission measuring 11 mm in diameter (Fig. 13-19), this was followed on June 13 with a width of 14 mm, June 20 with 22 mm, and Aug. 31 with 15 mm, at a time of clinical recovery. During the early course of the disease, thrombophlebitis occurred in the left leg. The roentgenograms of June 20 show, in addition to other changes, marked dilatation of the pulmonary artery with bulging of the second left curve. The original films of this series also show definite oligemia of the lung fields (not recognizable on these reproductions). The anticoagulant treatment was discontinued on Aug 22. On Sept. 7, another embolic episode with infarction occurred The second set (Fig. 13-20) includes four roentgenograms (dated Sept 7, 26, Oct. 20, and Jan 1, 1956), with the widths of the hilar artery measuring 20, 19, 18, and 13 mm, respectively In addition to the changing width, the convex lateral bulging is distinctly visible, even more so if compared with the first and eighth roentgenograms used as a normal base line

These roentgen signs immediately connected with pulmonary hypertension may be supported by the entire roentgen symptomatology of pulmonary embolism, one or several pulmonary infarcts, pleural effusion, and inhibited ventilation characterized by high position and diminished excursion of the diaphragm, basal atelectasis (often in the form of plate atelectasis), diminished translucency of the lower lung fields, and decreased distance between the horizontal interlobe and dome of the diaphragm

Thus, in the author's experience, the condition of acute cor pulmonale, i.e , acute pulmonary hypertension, can often be diagnosed, or at least suspected, on roentgenologic evidence

CHRONIC COR PULMONALE

Cor pulmonale may be defined as the effect upon the heart of increased work load, with

or without accompanying hypoxia, caused by morbid conditions of the lung parenchyma or pulmonary vascular bed. Among them, chronic pulmonary embolism is probably a more common cause than is generally recognized (Owen et al, O'Neal et al.). Chronic pulmonary embolism, leading first to paroxysmal episodes and eventually to persistent pulmonary hypertension, is probably the purest form of cor pulmonale, possibly corresponding to Cournand's low-output form versus the high-output types, dominated by hypoxia. These cases lend themselves not only to the study of the influence of pulmonary hypertension on the heart without complicating respiratory disturbances, but also to roentgenologic recognition and analysis, because of the absence of interfering structural changes in the lung fields.

In the posteroanterior view, the cardiac silhouette has great similarity with that found in mitral stenosis (Fig 13-21). There may be only moderate left dilatation of the silhouette, or none at all. The most prominent feature is *a bulge of the pulmonary artery* forming the second curve on the left, which may reach the stage of *aneurysmal dilatation*. The prominence is often better seen in the right oblique and lateral views. In the region of the third curve, a concavity is present instead of the convexity usually seen in mitral stenosis. All other signs of left atrial dilatation, including the displacement of the barium-filled esophagus, are also absent.

Dilatation of the right ventricle, if caused by increased resistance in the *periphery* (resistance dilatation or systolic overload), involves first the outflow tract (Zdansky). The elongation of the outflow tract lifts the pulmonic valve, and both the elongation and the dilatation of this tract contribute to the prominence of the pulmonary artery. They may also cause the right ventricle to participate in the contour of the silhouette above the left ventricle. The transverse diameter of the heart in the posteroanterior view is usually not increased *in the early stages*. Only when the dilatation involves the entire right ventricle, including the inflow tract, does the silhouette widen,

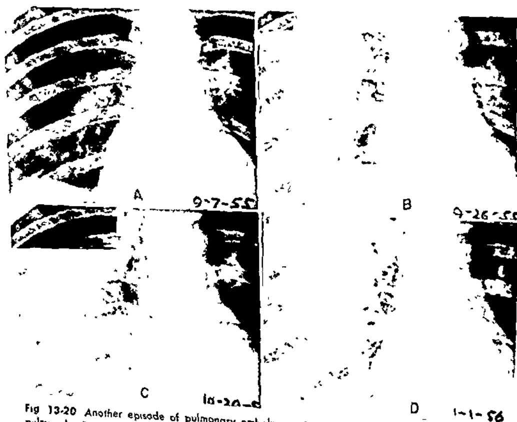


Fig 13-20 Another episode of pulmonary embolism with roentgenologic evidence of acute cor pulmonale. See text.

mainly to the left. In these instances, it may be difficult to discern whether or not there is additional left ventricular dilatation It is a common experience that dilatation of the left ventricle is assumed when none is found at autopsy. On the other hand, left ventricular dilatation may exist because of either independent preexisting heart disease or cor pulmonale. In these instances, the cardiac silhouette is usually dilated to the right. It should be mentioned that elevation of the cardiac apex, believed in the past to indicate right ventricular dilatation, has no such significance.

In the oblique and lateral views, an increase in thickness of the right ventricular wall from about 3 to 5 or 6 mm or more cannot be seen roentgenologically. On the other hand, a dilatation of the pulmonary artery, whether dynamic or organic, may be indirect evidence of ventricular hypertrophy Dilatation of the right ventricle can be assumed if, in the right anterior oblique view, the outflow tract of the right ventricle bulges forward In a similar way, the left anterior oblique view reveals an anterior bulge caused by the dilated right ventricular-atrial mass. If this bulge makes an angle of 140° or less with the supracardiac vascular contour, it can be safely assumed that it was formed in considerable part by the dilated right atrium with its appendage.

The *lateral views*, though most important, have not been given proper recognition for the assessment of the size of the right ventricle (Fig. 13-21A). In healthy persons, the area of contact between the heart and anterior chest wall, as seen on the lateral view, is usually less than a third of the distance between the sternoclavicular joint and the anterior attachment of the diaphragm This is true for a person of proportional build; chest deformities and abnormal position of the diaphragm limit the usefulness of this evaluation and should be taken into consideration.

Enlargement of the right ventricle increases the contact with the chest wall It has been objected that a normal-sized right ventricle may be pushed anteriorly by a dilated left atrium, thus obscuring the retrosternal space. This is hard to imagine on anatomic grounds and has never been demonstrated by angio-

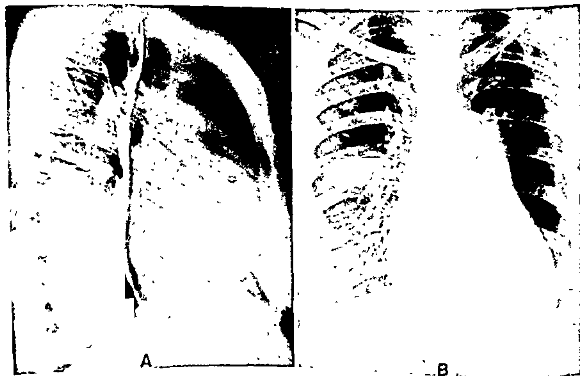


Fig. 13-21. Cor pulmonale due to chronic embolism in a 45-year-old female. Sudden onset of severe shortness of breath 1½ years before. Episodic repetition Died 2 years later. Post-mortem examination showed extreme right ventricular hypertrophy and dilatation Atheromatosis of the large branches of the pulmonary arteries Old and recent pulmonary emboli A few small fresh infarcts

cardiography. On the contrary, angiocardiography shows that a greatly hypertrophied and dilated right ventricle may cause backward displacement of the entire left heart, including the ventricle and atrium There is, however, another limitation of more academic nature It may occur that the right atrium and particularly its appendage, if dilated, may hug the right ventricle and thus add to the "area of contact." The same is true for the trunk of the dilated pulmonary artery, which may extend upwards the area of contact These conditions, however, are usually associated with right ventricular hypertrophy and dilatation Only in rare instances, such as tricuspid atresia or Ebstein's anomaly, a dilated right atrium occurs with a small right ventricle, and similarly an isolated dilatation of the pulmonary artery may occur with a normal right ventricle Thus, dilatation of the right ventricle, atrium, and pulmonary artery are usually tied together in their occurrence and functional significance, and it is of no practical consequence to discern how much each of the three components contributes to the enlarged cardiovascular body applied to the anterior chest wall such detailed morphologic analysis can be obtained only by angiocardiography.

Dilatation of the superior vena cava and azygos vein, corresponding to increased venous pressure and associated with right ventricular hypertrophy, dilatation, and failure, can be found in acute cor pulmonale

In addition to the cardiovascular silhouette, *the vascularity of the lung* fields is of diagnostic significance Prominent hilar shadows were mentioned in early descriptions of pulmonary emphysema, though their significance was not fully understood With better understanding of the pathophysiology of the pulmonary circulation has come the ability to *distinguish* the increased flow of blood to the lungs with *large arterial hilar arteries and wide peripheral pulmonary vessels* (the picture of the pleonemic lung, such as seen in the left-to-right shunts) from increased pulmonary arterial pressure with large hilar shadows and thin vascular markings (oligemic lung fields such as seen ...

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s ... of the pulmonary vessels, or a combination of both In some instances of pulmonary fibrosis and emphysema, these changes are limited to the most peripheral vessels while the branches of the third to fifth order are dilated.

Vasospasm of medium-sized and small arteries has been assumed to occur in acute cor pulmonale and in mitral stenosis. A vasospastic component, in addition to intimal thickening and hypertrophy of the media, is assumed to occur also in certain congenital heart diseases with left-to-right shunt.

The roentgenologist is inclined to attribute to *arteriospasm* a considerable part in the production of the oligemic lung field. The more radiolucent background, signalizing poor blood filling of the lung at the capillary level, would be the same, whether the diminished blood flow to the lung is caused by arteriosclerotic or spastic narrowing of the arteries The roentgen beam does not distinguish between vascular wall and blood-filled lumen, an artery in which the lumen makes eight-tenths, and the wall two-tenths of the over-all cross section casts the same shadow as another artery, of the same external width, in which the lumen is reduced to two-tenths and the wall thickened to eight-tenths of the over-all width. The narrowness of the vascular shadows therefore indicates over-all thinness. The arteries may be *collapsed because* an embolus, lodged proximally, obstructs the flow But in the absence of such gross mechanical obstruction, spasm of the arteries becomes irrefutable This is *confirmed* by the experience gained in cases of mitral stenosis where marked pulmonary *hypertension* is still reversible after valvulotomy

In cases of *primary pulmonary hypertension*, the roentgen appearance suggests similar disturbances in the vascular tree The arteries of the third to fourth order down to the arterioles seem to go into vasoconstriction, thus increasing the vascular resistance The larger hilar branches, sometimes described as elastic arteries *in contradistinction* to the muscular peripheral arteries, would respond to the increased arterial pressure with dilatation

In certain instances of subacute and chronic cor pulmonale, due to pulmonary embolism, plump hilar shadows are visible They are caused by large embolothrombi lodged in the hilar arteries (Hanelin and Eyler). They seldom fill the lumen of the vessel during life,

partly because the latter is maximally dilated. A cutoff appearance of the hilar shadow or the appearance of an "amputated tail" of the hilar shadow is sometimes caused by the edge of the embolus; in other cases this optical effect is enhanced by a crossing pulmonary vein.

In many instances of chronic pulmonary hypertension, an increase of pulse pressure can be revealed by fluoroscopy as exaggerated pulsation of the pulmonary artery and the hilar arteries. The arteriospasm appears to be reversible for a considerable time. When sclerotic changes, intima thickening, and media hypertrophy occur, the condition probably becomes irreversible, as in systemic hypertension.

Cor pulmonale has been observed in young children without parenchymal pulmonary disease. It is believed that the pulmonary vasculature of these cases has retained its fetal characteristics, thus imposing an additional load upon the right ventricle. The oligemic lung fields require differentiation from those of pulmonic stenosis, while concomitant left-sided failure with pulmonary congestion may be difficult to distinguish from a pleonemic lung due to a left-to-right shunt

Differential Diagnosis. While mitral valve disease can usually be ruled out by the absence of left atrial dilatation, the various congenital abnormalities associated with dilatation of the right ventricle and pulmonary artery, and especially those with pulmonary hypertension, should be considered This includes conditions with a left-to-right shunt (atrial and ventricular septal defects, patent ductus arteriosus, aortopulmonary fistula, and right-sided implantation of pulmonary veins) These conditions cause increased pulmonary flow of blood and a pleonemic lung field They may, however, be associated with pulmonary hypertension. Such a dynamic disturbance is common in Eisenmenger's complex, can be found in ventricular septal defect (25 per cent) and patent ductus arteriosus, and is rather rare in atrial septal defect (about 10 per cent) Other conditions are isolated pulmonic stenosis and multiple local stenoses in the pulmonary artery tree.

The oligemia of the lung fields, if generalized, may suggest pulmonary emphysema However, the typical gross chest deformities, including low position of the diaphragm, are absent, no structural changes in the lung can be seen, and the ventilation of the lung (fluoroscopy, pulmonary function tests) is normal If the oligemia is unilateral and associated with smallness of the half chest and with absence of the normal hilar and peripheral vascular tree, atresia of a pulmonary artery stem may be the underlying cause. Again, if the oligemia is unilateral or limited to a lobe, occlusion of the corresponding branch of the pulmonary artery by a thromboembolus is most likely.

COR PULMONALE WITH PARENCHYMAL DISEASE OF THE LUNG

The above description dealt with chronic cor pulmonale without parenchymal disease of the lung (so-called pulmonary hypertensive heart). The situation of chronic bronchitis, pulmonary emphysema, pulmonary fibrosis, and numerous other conditions should now be discussed. The complicated interplay of respiratory, circulatory, and hematologic adjustments creates conditions quite different from those producing the pulmonary hypertensive heart This form of cor pulmonale in the older person has been termed "pulmonary hypertensive heart disease with arterial oxygen desaturation" (Hecht) or, briefly, *emphysema heart.* The combination of morphologic and functional changes prevailing in a given instance can often be determined by functional studies but is usually not apparent on roentgenologic evidence. When marked pulmonary fibrosis with emphysema is present, one may assume that the heart is affected. However, severe emphysema may occur without gross evidence of pulmonary hypertension Chronic pulmonary hypertension may manifest itself on the roentgenogram by a dilatation of the pulmonary artery and of the hilar branches while the right ventricle has not yet undergone gross hypertrophy Thus, in pulmonary emphysema the heart not only may not be enlarged or show abnormal configuration but may be *strikingly small* (Fig 13-22) This impression is often exaggerated by the low position of the diaphragm This causes, in the anterior view, elongation and median position of the cardiac silhouette and may obscure dilatation of the pulmonary artery through a counterclockwise rotation In the lateral view, the emphysematous anterior edges of the lung are interposed between heart and anterior chest

wall, thus depriving one of the yardstick of the area of contact On the contrary, in the elongated, emphysematous chest, the dilated left pulmonary artery may stand out in the left anterior oblique or lateral view, running posteriorly as a wide arc, subdividing the aortic window and forming a "double window" In similar fashion, the dilated right pulmonary artery may be recognized in this projection, in head-on view, crossing in front of the trachea Often the pattern of cor pulmonale is not obvious at first glance. The oligemia of the peripheral lung fields is often completely submerged under the consolidation of diffuse fibrosis Moreover, in advanced cases with bullous emphysema, it is impossible to say whether the obvious oligemia is part of the emphysematous destruction of the lung or the condition of secondary cor pulmonale.

Thus, it is generally accepted that a complete roentgenologic picture of chronic cor pulmonale is not always present or recognizable in parenchymatous pulmonary disease. Dilated hilar arteries and pulmonary trunk with large pulsations are sometimes the only signs suggesting chronic cor pulmonale

In chronic diseases, whenever the clinical picture or the roentgen findings point to chronic pulmonary disease, it is useful to search for the following signs of cor pulmonale: slight fullness in the region of the pulmonary artery on the left; in the presence of large hilar shadows, one should ascertain whether they are solid masses or dilated arteries (expansive pulsation on fluoroscopy). If previous roentgenograms are available, a comparison is helpful A set of films may reveal a progressive dilatation of the pulmonary artery trunk or its hilar branches, and return to normal.

Marked, chronic pulmonary *hypertension* may occur in various types of heart disease, such as hypertensive heart disease or rheumatic aortic lesions, *owing to complicating* pulmonary disease or chronic pulmonary embolism The roentgen appearance of the underlying disease is then modified by features of cor pulmonale, mostly consisting of plump *hilar arteries* and oligemia of the lung fields. In describing such a condition, one may speak of "aortic stenosis with complicating cor pulmonale"



Fig 13-22. "Emphysema heart" in a 58-year-old male. The posteroanterior view shows the prominent pulmonary artery; the left oblique view shows the "double window" The heart is small.

Circulation times in cor pulmonale

WILLIAM M. HITZIG

ASTHMA

The differentiation of cardiogenic dyspnea from bronchogenic asthma is one of the most difficult problems at the bedside, especially when the symptom manifests itself for the first time in patients in the fifth to the seventh decades of life. The simple performance of the circulation time at the bedside with Decholin, calcium, or saccharin may rapidly impart to the clinician the obvious diagnosis and allow for immediate and appropriate treatment for the relief of the asthma. Thus, a prolonged circulation time ("arm-to-tongue" time of 20 to 40 sec) in the presence of dyspnea proves it to be of cardiac origin This finding immediately counterindicates the use of epinephrine and indicates the prompt use of morphine, which, on the other hand, should not be employed in bronchial asthma In bronchial asthma, with or without severe emphysema, both the "arm-to-lung" time and the "arm-to-tongue" time may be either reduced or found to be within the range of normal circulation time.

DYSPNEA AND ORTHOPNEA

These manifestations of respiratory stress may be part and parcel of intrinsic pulmonary disease with varying degrees of associated obstructive ventilatory and diffusion insufficiencies. To differentiate from the respiratory difficulties that manifest themselves in the course of cardiac disease, the circulation time may serve as a guide in excluding the pulmonary arterial hypoxia that accompanies chronic emphysema, unilateral absence of a lung, complete unilateral pneumothorax, interstitial pulmonary fibrosis, and allied pulmonary conditions In these instances, the velocity of blood flow may actually be increased as a compensatory mechanism, and the circulation time may be either diminished or within the normal range, whereas in dyspnea or orthopnea of congestive heart failure the circulation time is prolonged

7

Primary pulmonary hypertension

DAVID T. DRESDALE

Primary pulmonary hypertension, a condition in which there is an elevated pulmonary artery pressure without a demonstrable cause, is rare, although more frequently recognized since the advent of cardiac catheterization. A more common condition is pulmonary hypertension secondary to other conditions such as rheumatic mitral valvular disease, left heart failure, chronic pulmonary disease, congenital heart disease (especially those forms with increased pulmonary blood flow), diffuse pulmonary embolism, kyphoscoliotic heart disease, and specific affections of the pulmonary vascular bed. In such cases the condition is known as *secondary* pulmonary hypertension

The etiology of primary pulmonary hypertension is not known There is considerable evidence that the increased resistance in the pulmonary vascular bed occurs in the precapillary vessels, but the cause is speculative The possibility of vasomotor activity is suggested by (1) evidence of nerve endings present in the muscular walls of small pulmonary arteries, and (2) the effect of certain drugs on the pulmonary vascular resistance. Dresdale et al (1954) and Hecht, using *Priscoline*, an adrenolytic and sympatholytic agent, observed in acute experiments a definite reduction in pulmonary vascular resistance This has also been noted by Davies et al and by Fowler et al (1950), using tetraethylammonium chloride, a ganglionic blocking agent More recently Wood (1958) and Fritts et al. (1958), brought about a reduction of the pulmonary vascular resistance in primary pulmonary hypertension, secondary pulmonary hypertension, and anoxia-induced pulmonary hypertension, with acetylcholine injected directly into the pulmonary vascular bed through a cardiac catheter. On the other hand, sympathectomy and hilar plexectomy (Griswold, Cooley—quoted from Chapman et al., 1957) did not have any beneficial effect. Hypoxia, which can cause a rise in pulmonary vascular resistance, is not a factor here since the majority of cases do not have arterial oxygen unsaturation More recently *serotonin* (5-hydroxytryptamine) has been shown to cause marked pulmonary vasoconstriction when infused into the pulmonary artery of dogs (Borst et al.). Its place, if any, in primary pulmonary hypertension has yet to be established. Edwards et al, Shephard et al., and Evans et al believe that, in some instances, there may be a persistence of a narrowed fetal pulmonary vasculature, i.e, *medial hypertrophy of the muscular arteries.* Most of the cases of primary pulmonary hypertension show pulmonary vascular changes which undoubtedly, when developed, contribute to the pulmonary vascular resistance. However, since it is felt that these lesions are secondary to pulmonary hypertension (see Chaps. 1 and 8), they are not thought of as the initiating agent in primary pulmonary hypertension.

At necropsy, all cases of primary pulmonary hypertension show marked right ventricular hypertrophy, but the changes in the pulmonary vascular bed may vary from none or minimal to marked (Dresdale et al, 1954, Soothill, Evans et al) Because of the absence of any changes in the pulmonary vascular bed, De Navasquez et al. (1940), before cardiac

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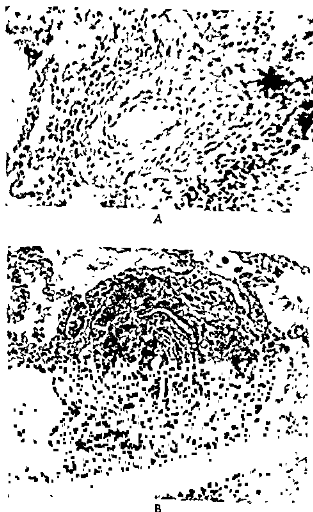


Fig. 13-23. A Fibrous intimal thickening of an arteriole of the lung. B. Occlusion of an arteriole of the lung by cellular tissue (thrombosis or intimal reaction?).

catheterization, preferred to designate their cases of isolated right ventricular hypertrophy found at autopsy, "idiopathic right ventricular hypertrophy" On the other hand, some authors called their cases "primary pulmonary vascular sclerosis" (Evans et al) or "obliterative pulmonary arteriosclerosis" (Stuckey) because of the severity of pulmonary vascular changes

The changes in the pulmonary vascular bed described below are not limited to primary pulmonary hypertension They also have been described in cases of secondary pulmonary hypertension, specifically congenital heart disease and mitral stenosis (Larrabee et al.; Edwards, Heath et al, 1955b, Parker et al, 1958) When pulmonary vascular changes occur, they are found proximal to the capillaries Predominant changes of the stem and large elastic arteries are *atheromatous lesions* It is common to find an abnormality (Heath et al, 1955a) consisting of *a distinct muscular media* in the elastic arterioles less than 100 μ in diameter (normally, in the adult, they have only a single elastic lamina between intima and adventitia). There also is fibrous intimal thickening (Fig. 13-23A), which may be severe enough to cause occlusion of the arterioles In conjunction with the above changes, there may be *medial hypertrophy in the muscular arteries*. Medial hypertrophy of the muscular arteries alone, suggesting the persistence of the fetal characteristics of the pulmonary arteries, has been described (Shephard et al, 1957, Wade et al.). At times, the muscular arteries, the arterioles, or both are partially or wholly occluded by an abnormal sparsely cellular tissue (Fig. 13-23B), which histologically may be interpreted as of thrombotic origin or as the result of intimal reaction (Evans et al). These lesions in various stages of organization have been seen in the precapillary and postcapillary vessels of microscopic size (Dresdale et al., 1951). Similar lesions have been described in 90 per cent of the cases of tetralogy of Fallot (Rich) and in pulmonary vessels of long-standing mitral stenosis with pulmonary hypertension (Larrabee et al). The question frequently and justifiably raised is whether the thrombotic lesions are related to emboli and whether they cause the pulmonary hypertension In the majority of cases reported, sites for release or discharge of emboli are not found at necropsy. It also would be very difficult to postulate multiple pulmonary emboli in young patients who develop pulmonary hypertension of unknown etiology, and in congenital heart disease, especially tetralogy of Fallot Recently Dammann et al. were able to produce similar lesions in the pulmonary vascular tree of dogs by subjecting the pulmonary vessels to a high pressure These changes were complete 11 weeks after the subclavian artery was anastomosed to the pulmonary artery of the upper lobe of the left lung. *Medial necroses* have also been reported in muscular pulmonary arteries and pulmonary arterioles (Heath et al, 1957) *Necrotizing arteritis* was noted by Shephard et al. (1957) in two cases, and was thought to be secondary to the presence of pulmonary hypertension. Similar changes have been described in four cases of

right ventricular failure of unknown etiology (Mc Keown), in the pulmonary hypertension of Eisenmenger's complex (Mc Keown; Symmers), and in pulmonary hypertension secondary to mitrol stenosis (Parker et al., 1936, Dammann et al). In view of the evidence that changes in the pulmonary vascular bed may occur when there is pulmonary hypertension regardless of the cause, it would not be unreasonable to suggest that the lesions of the pulmonary vascular bed in primary pulmonary hypertension are *the result*, rather than the cause, of the elevated pulmonary artery pressure

Primary pulmonary hypertension has been found in all age groups, having been described in patients as young as 20 months and as old as 74 years The majority of patients, however, are under the age of 40, mainly in the 20- to 40-year-old age group The *sex* incidence is predominantly female. A *familial tendency* is suggested by the findings of this disease in a woman, her sister, and her son (Dresdale et al., 1954) A brother of the woman was reported to have died of an undiagnosed heart disease at an early age

Although there are no symptoms specific for primary pulmonary hypertension, there is a group of symptoms that should raise suspicion of the presence of this disease The predominant symptoms in order of frequency of occurrence are (1) exertional dyspnea and weakness, (2) substernal and left chest pain simulating coronary insufficiency, (3) exertional syncope, and (4) palpitation Exertional dyspnea and weakness, usually the first and dominant symptoms, may be related to the decrease of right heart reserve Heath et al. (1955a) suggest that the dyspnea is due to anatomic changes in the pulmonary vessels. Some cases have been reported, however (Wittenborg, McGuire et al ; Soothill; Evans et al), in which these symptoms were present but in which no significant changes in the pulmonary vascular bed were found at necropsy *An anginal type of pain*, occurring in approximately 25 to 30 per cent of the patients, is frequently associated with exertion but may occur at rest (Evans et al). This chest pain is not limited to patients with primary pulmonary hypertension. It occurs also in other diseases with the secondary type of pulmonary hypertension (Viar et al ; Stuckey) and in patients with isolated right ventricular hypertrophy secondary to pulmonic stenosis (Stuckey, Lowance et al.; Abrahams et al ; Lasser et al). A decreased cardiac output and inadequate coronary blood flow during exercise (Dresdale et al , 1951; Stuckey) may be the explanation for this, since coronary artery disease is not found at autopsy. The decrease in cardiac output on exertion is also associated with a marked increase in the right ventricular diastolic pressure, which would further cause an increase in resistance to coronary blood flow in the right ventricle during diastole. The existence of precordial pain in the presence of pulmonic stenosis would not support the thesis that it is caused by distention of the pulmonary artery due to high tension (Viar et al.). *Exertional syncope* (Dresdale et al , 1951; Dressler; Evans et al), occurring in at least 25 per cent of the patients, appears to be related to acute right heart failure and cerebral ischemia. Cardiac arrhythmias are rare, but occasionally atrial fibrillation is present terminally. Orthopnea and paroxysmal dyspnea have been described (Evans et al.) but are unusual. When orthopnea, paroxysmal dyspnea, or hemoptysis is present, the diagnosis of primary pulmonary hypertension must be held in abeyance, since pulmonary edema does not occur in these patients. When pulmonary infarction is found, embolic phenomena must be considered.

The pertinent *physical findings* are limited to the heart and those organs affected by an elevated venous pressure as a result of right heart failure. *Right ventricular hypertrophy*, characterized by increased retrosternal dullness, widening of the conus area, and a distinct pulsating bulge of the precordium most marked along the left margin of the sternum, is always present. *The second pulmonic sound is markedly accentuated and usually split.* Early in the disease there may be no murmurs. When they occur later, there may be *a blowing systolic murmur over* the apex and precordium, owing to relative tricuspid insufficiency, and over the pulmonic area, due to a dilated pulmonary artery. A *diastolic murmur* in the pulmonic area and along the left sternal border (*Graham-Steell murmur*) can be heard in a large number of cases because of a functional pulmonary valvular insufficiency due to dilatation of the pulmonary valve ring Occasionally, a diastolic murmur or a diastolic



Fig. 13-23. A. Fibrous intimal thickening of an arteriole of the lung. B. Occlusion of an arteriole of the lung by cellular tissue (thrombosis or intimal reaction?).

catheterization, preferred to designate their cases of isolated right ventricular hypertrophy found at autopsy, "idiopathic right ventricular hypertrophy." On the other hand, some authors called their cases "primary pulmonary vascular sclerosis" (Evans et al) or "obliterative pulmonary arteriosclerosis" (Stuckey) because of the severity of pulmonary vascular changes.

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tion curves (Shephard et al, 1957) unless there is a patent foramen ovale or bronchopulmonary anastomoses The pulmonary "arteriolar" resistance is very high. Figure 13-24 demonstrates the hemodynamic data obtained in three patients with primary pulmonary hypertension, the diagnosis being confirmed by necropsy in two of them

The *electrocardiogram* shows changes characteristic of right ventricular hypertrophy as well as evidence of right atrial hypertrophy.

The *x-ray findings* (Fig 13-25) are similar to those in conditions with right ventricular hypertrophy and diminished pulmonary blood flow without evidence of pulmonary parenchymal disease The characteristic findings are (1) right ventricular enlargement, (2) bulging pulmonary artery segment, (3) prominent hilar vessels, and (4) normal or decreased intrapulmonary vascular markings There should be no evidence of left atrial enlargement Overlapping of the spine by the cardiac silhouette may occur in the left anterior oblique view, but this in the presence of marked right ventricular hypertrophy does not necessarily denote left ventricular enlargement At autopsy, the patient whose x-rays are shown in Fig 13-25 had a normal left atrium, left ventricle, and mitral valve.

The disease generally runs a malignant *course* of from 5 months to 5 years, with the average course of 2 to 3 years after the onset of congestive heart failure Cases are reported in which the patient lived as long as 7 (Evans et al) and 15 years (Mc Callum) The course is usually progressively downhill, it is characterized by right heart failure, not infrequently terminating in sudden death. These patients do not tolerate procedures well Deaths have been reported during or following cardiac catheterization (Schafer et al; Cutler et al.); after other procedures, such as determination of decholin circulation time, angiocardiography (Cutler et al.), and simple exercise test (Wade et al); and during induction of anesthetics (Inkley et al).

Primary pulmonary hypertension should be differentiated from any condition in which there is evidence of right ventricular hypertrophy, pulmonary hypertension, and clear lung fields.

Cardiac catheterization is helpful in eliminating cases of acyanotic congenital heart lesions with pulmonary hypertension and pulmonic stenosis with poststenotic dilatation of the pulmonary artery. *Dye-dilution curves* made at the time of cardiac catheterization or angiocardiography can exclude most of the cyanotic congenital heart disease cases, except for those with an interatrial septal defect and reversed (*right-to-left*) *shunt*. It is extremely difficult to differentiate primary pulmonary hypertension with patent foramen ovale and right-to-left shunt from interatrial septal defect with right-to-left shunt, unless the latter, during cardiac catheterization, also exhibits a left-to-right *shunt*.

Recurrent pulmonary emboli and conditions in which there is specific involvement of the pulmonary vessels, such as parasitic infestations (schistosomiasis), lymphangitic carcinomatosis, and necrotizing pulmonary arte-

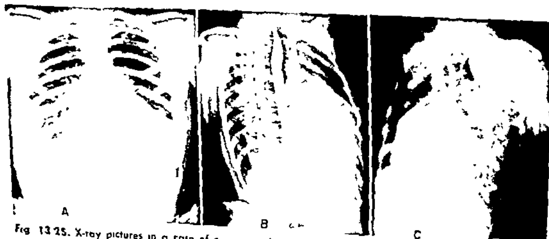


Fig 13-25. X-ray pictures in a case of primary pulmonary hypertension confirmed by autopsy.

3d sound resembling a mitral opening snap is present at the apex These sounds can be easily differentiated from that heard in mitral stenosis by means of phonocardiography. Since all the patients eventually develop congestive right heart failure, protracted neck vein distention, with visible giant A waves, is present and associated with hepatomegaly. Frequently, there is a pronounced *presystolic liver pulsation,* which becomes even more pronounced when fused with the systolic pulsation in the presence of tricuspid insufficiency. Peripheral edema may appear late (Dresdale et al, 1951). The peripheral arterial pulse is of poor volume or normal. The systemic blood pressure is always normal or low. Various degrees of *cyanosis* without clubbing of the toes or fingers may be seen This cyanosis is usually unassociated with arterial hypoxemia and is the result of an increased arteriovenous oxygen difference due to decreased cardiac output When arterial unsaturation occurs, it is the result of either a patent foramen ovale with right-to-left shunt or of a shunt through large bronchopulmonary anastomoses (Evans et al).

Routine laboratory findings are normal except for occasional *slight polycythemia.* Pulmonary function results are generally within normal limits.

Hemodynamic studies at rest utilizing the technique of right heart catheterization show (1) markedly elevated pulmonary artery pressure; (2) normal pulmonary arterial "wedge" pressure, (3) normal or low systemic artery pressure; (4) elevated right ventricular end-diastolic pressure, frequently present before clinical signs of right heart failure, (5) low cardiac output; (6) increased arteriovenous oxygen difference; (7) normal arterial oxygen saturation; and (8) normal arterial dye-dilu-

	Normal	G.N.	M.K.	M.R.
Arterial Blood Oxygen Saturation (%)	96.2±1.2	97.8	96.4	98.4
Oxygen Consumption (cc/min./m² B.S.A.)	115–135	144	109	127
Arterial-venous Difference (Vol. %)	3.5–5	5.9	6.9	8.3
Cardiac Index (L./min./m² B.S.A.)	3.1±0.4	2.44	1.59	1.53
Stroke Volume (cc)	60–80	48	29	23
Total Blood Volume (cc/m² B.S.A.)	2,670	2,710	2,615	3,550
Hematocrit (%)	40	40	40.5	47

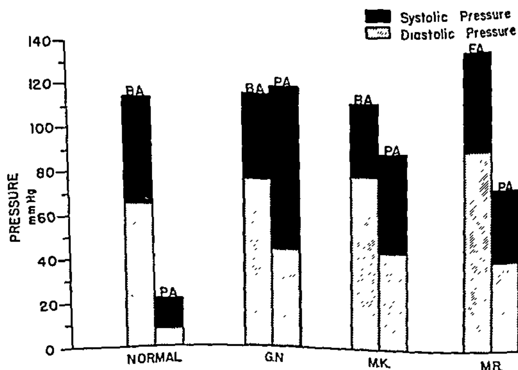


Fig. 13-24. Hemodynamic data from three patients with primary pulmonary hypertension. Peripheral (BA) and pulmonary (PA) pressures.

8

Clinical aspects of cor pulmonale

Acute Cor Pulmonale
Chronic Cor Pulmonale

IRVING MACK

ACUTE COR PULMONALE

Acute cor pulmonale may be defined as acute right heart "strain" caused by a sudden marked increase in the work demanded of the right ventricle, left ventricular failure being excluded This increased work ordinarily results from *an abrupt increase in resistance to blood flow in the pulmonary circulation* Although the commonest cause of acute cor pulmonale is pulmonary embolism (McGinn and White, 1935), the two terms should not be used interchangeably *Pulmonary embolism does not always cause acute cor pulmonale* Furthermore, there are other causes for acute cor pulmonale besides pulmonary embolism Any condition imposing a sudden increased load (input as well as output) on the right ventricle may cause the same hemodynamic changes, the same clinical picture, and the same electrocardiographic findings as those found in acute cor pulmonale due to pulmonary embolism Thus, acute cor pulmonale may occur in patients in whom massive destructive pulmonary disease is complicated by sudden further obliteration of the pulmonary vascular bed, such as that caused by extirpative or collapse surgery, spontaneous pneumothorax, massive atelectasis, or extensive pneumonitis (Mack et al, 1950a) *A combination of events may lead to acute cor pulmonale* Patients have been described with compression of the main pulmonary artery trunk or its major stems by a tumor, who, with the sudden onset of massive pneumonitis or extensive metastatic involvement of the remaining pulmonary tissue, developed fatal acute cor pulmonale (Mack et al, 1950a) Acute cor pulmonale has also been reported resulting from acute spontaneous mediastinal emphysema (Klein, 1947) or a sudden increase in the herniation of intestinal content through a diaphragmatic hernia (McGinn and Spear, 1941) The sudden development of a left-to-right shunt will lead to all the abnormalities recognized as acute cor pulmonale This applies to patients in whom an aneurysm of the aorta or sinus of Valsalva suddenly ruptures into the right atrium, ventricle, or pulmonary artery, and to those in whom a sudden interventricular septal perforation occurs, as in acute ulcerative bacterial endocarditis or interventricular septal rupture following an infarction.

While pulmonary emboli are usually blood clots detached from other portions of the circulatory system (various areas of the venous bed or the right chambers of the heart), acute cor pulmonale may also be caused by embolism of fat, air, amniotic fluid, or cerebral cortical tissue (Durant et al., 1947, Warren, 1946; Steiner and Lushbaugh, 1941, Oppenheimer, 1954). Acute cor pulmonale does not occur in every case of pulmonary embolism, the number and size of the emboli may be insufficient to cause the acute hemodynamic changes leading to acute cor pulmonale, or the embolization may lead to ventricular fibrillation and sudden death (Katz, 1945)

Patients surviving repeated widespread embolization of the lungs may later develop chronic cor pulmonale (Owen et al., 1953). This may occur after repeated, multiple, small pulmonary embolizations, or after occlusion, with subsequent thrombosis, of large branches

ritis, have hemodynamics similar to that found in primary pulmonary hypertension. Clinical findings, as well as lung biopsy, may be helpful

At times, the diagnosis is not established definitively until autopsy. Even then, the pulmonary vascular changes secondary to pulmonary hypertension make it difficult to separate recurrent small pulmonary emboli from primary pulmonary hypertension unless a source for the emboli is found Patients with idiopathic dilatation of the pulmonary artery do not have evidence of right ventricular hypertrophy. The elevated pulmonary artery "wedge" pressure and enlargement of the left atrium found in mitral stenosis are not present in primary pulmonary hypertension In primary pulmonary hypertension, there is no evidence of pulmonary parenchymal involvement like that found in cor pulmonale secondary to pulmonary disease.

There is no treatment, as yet, that will reverse the malignant course of the disease. *Priscoline,* 50 to 75 mg parenterally, several times a day, has temporarily improved some of the patients clinically and hemodynamically (Dresdale et al., 1951; Hecht). Thoracic sympathectomy and hilar plexectomy (Griswold, Cooley, quoted from Chapman, et al, 1957) have not been beneficial. Anticoagulant treatment, suggested by Cutler et al., could be useful if the obstructive lesions in the pulmonary blood vessels were predominantly thrombotic and not due to proliferation of intimal fibroelastic tissue. Although the response to the accepted treatment for heart failure is poor, it should be instituted when right heart failure is present.

left lateral position may be lifesaving (Durant et al., 1954).

REFLEX PULMONARY ARTERIOLAR CONSTRICTION. Obstruction of small pulmonary arteries and arterioles by showers of emboli leads to reflex arteriolar constriction, not only in the same lobe but also in the opposite lung. This parallels the situation seen in embolization of major systemic arteries (Megibow et al., 1942, De Takats et al., 1939, Laurent et al., 1956). Additional evidence for this pulmono-pulmonary reflex was obtained by Niden and Aviado by using a perfusion technique, in which one lobe of the dog's lung was supplied with blood from a donor dog. Injection of glass beads into the unperfused lobes of the experimental dog produced a reflex vasoconstriction of the perfused lobe, although the beads never reached the perfused lobe (Niden and Aviado, 1956). Mention should be made that other investigators have not demonstrated the above reflex pulmonary vasoconstriction (Daley et al., 1951; Knisely et al., 1957).

ELEVATION OF PULMONARY VENOUS PRESSURE. There is some evidence that a reflex elevation of pulmonary venous pressure may add to the increase in pulmonary vascular resistance (Aviado and Schmidt, 1955, Laurent et al., 1956).

HUMORAL MECHANISMS. It has been suggested that the liberation of chemical substances, such as serotonin, at the site of embolism may also act to increase pulmonary vascular resistance. The presence of increased circulating serotonin during embolism has been confirmed (Comroe et al., 1953, Aviado and Schmidt, 1955).

HYPOXEMIA. Hypoxemia has been shown to cause an increase in pulmonary arterial blood pressure by some, as yet, poorly understood mechanism, which is discussed below (*see* Chronic Cor Pulmonale).

The development of dilatation of the right ventricle leads to a change in position of the entire heart, *viz.*, clockwise rotation about its longitudinal axis, as well as a more vertical position (McGinn and White, 1935, Wilson et al., 1947).

Mechanism of the Production of Myocardial Ischemia. Myocardial ischemia occurs in acute *cor pulmonale* as a result of a reduction in coronary flow, hypoxemia, and an increased oxygen requirement of the heart as a result of its increased work.

REDUCED CORONARY FLOW. The reduction in the coronary arterial flow is due to multiple factors. The increased pulmonary resistance causes a rise in right ventricular pressure and dilatation of that chamber. The increased pressures within the right ventricle (and often the right atrium), by interfering with the drainage from the thebesian vessels and the coronary sinus, reduce the effective pressure gradient between the coronary arteries and their drainage systems.[1] The associated increased intramural pressure of the right ventricle, acting as an extravascular force, further impedes coronary blood flow in the walls of this chamber. Since this reduction of blood flow is most marked in the right coronary artery, the evidence of myocardial ischemia is most marked in the right ventricle and the posterior portion of the left ventricle (Katz et al., 1938; Currens and Barnes, 1943, Durant et al., 1947).

A marked *fall in systemic arterial blood pressure* has been noted to occur after pulmonary embolism, and is frequently disastrous, since it decreases the effective pressure gradient between the aorta and the coronary arteries and their drainage systems. This acute arterial hypotension is due to a combination of various factors. The immediate systemic arterial hypotension following pulmonary embolization is part of a triad caused by a Bezold-Jarisch-like reflex (apnea, bradycardia, and hypotension), possibly due to the stimulation of pressoreceptors in the heart and lung. Experimentally, it can be abolished by vagotomy (Niden and Aviado, 1956). That shock in acute *cor pulmonale* may be due to such a reflex mechanism has been demonstrated in man (Selzer and Bradley, 1957). However, the continued hypotension results mainly from the diminished output of the left ventricle, which is a consequence of the obstruction to blood flow in the pulmonary circuit (reduced left ventricular inflow) (Mendlowitz, 1938, Katz et al., 1945). Moreover, this diminished cardiac output per se decreases coronary flow. Increased pulmonary venous pressure, which has been observed

[1] Increased right atrial pressure occurs only when the diastolic pressure of the right ventricle rises. Therefore, it is evidence of right ventricular failure.

of the pulmonary artery (Hanelin and Eyler, 1951; Magidson and Jacobson, 1955; Ring and Bakke, 1955).

INCIDENCE

In most general hospitals, pulmonary embolism is found in about 10 per cent of patients at necropsy (Short, 1952; Hampton and Castleman, 1940). An even higher incidence (25 per cent) is recorded when a more selected group is studied, as in necropsies in a home for the indigent (Tobin, 1954). Clinical surveys show lower figures mainly because of the difficulties in diagnosis In some hospitals, the diagnosis of nonfatal pulmonary embolism is rarely made Israel and Goldstein report that pulmonary embolism occurred in 1.2 per cent of medical admissions and in 0.6 per cent of surgical admissions to a general hospital The frequency of pulmonary embolism is thus greater in medical patients, but it should be kept in mind that the age of this group is higher In some hospitals, pulmonary embolism is the most common acute pulmonary disease, more prevalent than lobar pneumonia or bronchogenic carcinoma (Short, 1952, Israel and Goldstein, 1957)

Pulmonary embolism occurs most frequently in those conditions associated with immobilization, venous trauma (mechanical or infectious), and the hypercoagulable state While *postoperative embolism* has been observed in patients without demonstrable predisposition, it occurs much more frequently in the presence of dehydration, obesity, heart disease, venous varicosities, previous thrombophlebitis, anemia, and neoplasm. *Thrombophlebitis*, with or without much inflammatory manifestation, predisposes to pulmonary emboli Thrombophlebitis may occur at the site of fractures, nonpenetrating injuries, and after repeated venipuncture. Predisposing to pulmonary embolism are such medical diseases as congestive heart failure, polycythemia vera, severe anemia, and neoplasm. Pulmonary embolism is much more common after the age of 40 (Israel and Goldstein, 1957).

PATHOLOGIC PHYSIOLOGY OF ACUTE COR PULMONALE

Originally, the disturbed physiology, the clinical picture, and the electrocardiographic changes of acute cor pulmonale were considered primarily a reflection of the dilatation of the right ventricle resulting from the increased burden imposed upon this chamber (McGinn and White, 1935). However, *the additional factor of myocardial ischemia, particularly of the right ventricle and posterior wall of the left ventricle, is of equal importance.* Indeed, acute or subacute myocardial necrosis of varying extent is not infrequently seen at necropsy in patients who die in acute cor pulmonale They occur only when the myocardial ischemia is sufficiently severe and prolonged. While this necrosis is reported to occur occasionally in the absence of significant narrowing of the coronary arteries, it is usually favored by (1) duration of life for several hours or weeks after the initial embolization, (2) preexisting coronary sclerosis, (3) previous hypertrophy of the heart which accentuates any coronary insufficiency (coronary flow/muscle mass disproportion) (Horn et al., 1939; Megibow et al., 1942; Dack et al., 1949).

Mechanism of the Right Ventricular Dilatation. The sudden increase in resistance to pulmonary flow in acute cor pulmonale results from the following events:

MECHANICAL OBSTRUCTION OF VESSELS The pulmonary emboli may vary in size from the large *serpentine embolus,* often coiled up and riding the bifurcation of the pulmonary artery trunk or occluding its main branches, to smaller emboli occluding the smaller pulmonary arteries, or even very minute ones plugging the arterioles The emboli often are detached from their source of origin in volleys. In pulmonary *air embolism*, the catastrophic events result from a different mechanism Death, when it occurs, is due to obstruction of the right ventricular outflow tract by an air trap which forms within it. Durant has demonstrated experimentally in dogs that turning the animal onto his left side so that the outflow tract will assume a position inferior to the body of the right ventricle permits the air trap to disappear from this now inferior position, it becomes churned into a froth which gradually disappears from the cavity of the right ventricle by being transported with the blood to the lungs, where excretion can take place This relieves the obstruction Thus, *displacement of the air trap by turning the body into the*

INCREASED OXYGEN REQUIREMENT OF THE HEART AS A RESULT OF ITS INCREASED WORK. The work of the heart in acute cor pulmonale must increase in order to overcome the greater resistance in the pulmonary circuit. Tachycardia may also further tax the heart. Since the oxygen requirement of heart muscle increases at least in proportion to the amount of work performed and the degree of dilatation (Landowne and Katz, 1944, Bing et al, 1949), the relative ischemia is intensified in the presence of a diminishing supply of oxygen to the heart. Significant *fever*, while unusual as an early manifestation of acute cor pulmonale due to embolism, frequently occurs later and tends to increase the oxygen requirements of the peripheral tissues as well as those of the heart.

It is the ultimate inability of the heart to meet these increased demands for work in the presence of relative ischemia that eventually results in failure and death in acute cor pulmonale

Elliott and Beamish have pointed out that *in the presence of a patent foramen ovale, pulmonary embolism may cause a right-to-left shunt through the defect which serves to alleviate the effects of the embolism* The full clinical sequence consists of pulmonary embolism, followed by a variable period of improvement (the "palliative-shunt" phase), and finally by sudden death when the shunt is occluded In its most recognizable form, the shunt phase is characterized by pallor, cyanosis unrelieved by oxygen, hypotension, profuse perspiration, moderate venous distention, and absence of the usual electrocardiographic changes seen in acute cor pulmonale During this phase, *peripheral paradoxic embolism* may occur because there is a functioning interatrial shunt with a sizable right-to-left flow of blood In the reported cases, death was precipitated by acute cor pulmonale as a consequence of sudden obstruction of this decompressive shunt between the right and left atria, and not to further pulmonary embolism, as had been supposed (Elliott and Beamish, 1953)

DEVELOPMENT OF PULMONARY INFARCTION

Nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed The bronchial arterial circulation is not necessary for this purpose (Karsner and Ghoreyeb, 1913). It has been observed clinically and confirmed experimentally that *pulmonary congestion favors the development of pulmonary infarction* after pulmonary embolism (Chapman et al., 1949). However, even in the absence of pulmonary venous congestion, when sufficient emboli are present to produce complete obstruction of the pulmonary arterial blood supply to a segment of pulmonary tissue, or if a large enough pulmonary artery is occluded, infarcts do occur (Steinberg and Mundy, 1936). When fewer emboli are discharged, instead of true pulmonary infarcts, lesions exhibiting the edema, alveolar hemorrhage, and leucocytic infiltration, corresponding to the "incomplete infarcts" are encountered (Hampton and Castleman, 1940). The *bronchial arterial circulation* is an important contributing factor to the development of hemorrhage into pulmonary tissue after pulmonary embolism. However, experimentally, if sufficiently severe pulmonary venous congestion is present, pulmonary infarcts develop even after the bronchial arteries are occluded to the area before the emboli are produced (Ellis et al, 1952a) Since infection frequently helps to cause excavation and the production of *infarct cavities*, it is important to use antibiotic therapy in patients with pulmonary embolism Infected pulmonary infarcts, because of their contiguity with pleural surfaces, are not infrequently complicated by the development of *empyema*

CLINICAL FINDINGS

The clinical picture of pulmonary embolism may vary greatly While embolization of the lung may be entirely *silent*, a high index of suspicion in the examiner will permit the diagnosis to be made much more frequently than heretofore reported Important are the size, number, location, and frequency of recurrence of the [illegible]

[illegible]

[illegible] *of pulmonary infarction.*

Manifestations of pulmonary embolism include dyspnea, tachypnea, retrosternal *pressure* pain, tachycardia, signs of cerebral *ischemia* (restlessness, syncope, convulsions) [illegible]

experimentally in pulmonary embolization, is known to cause peripheral vasodilatation by a poorly understood mechanism, which can be abolished by vagotomy (Niden and Aviado, 1956). Prolonged hypoxemia also contributes to the peripheral circulatory collapse.

While not usually recognized clinically, *bradycardia* develops immediately after embolization. This is a result of a Bezold-Jarisch-like reflex, as well as a result of the stimulation of pressoreceptors in the trunk of the main pulmonary artery (Niden and Aviado, 1956). *Tachycardia* soon supervenes and becomes one of the most outstanding and persistent clinical findings. It is a result of the hypoxemia and of reflexes arising from stimulation of carotid and aortic receptors Although initially of compensatory value, tachycardia may lead ultimately to a further reduction in cardiac output and so, secondarily, to a diminution of the coronary flow by decreasing the duration of diastole

Various reflexes, which directly diminish coronary flow in acute cor pulmonale, have also been described. However, the existence of a so-called *pulmonocoronary reflex*, in which reflex vagal coronary vasoconstriction is allegedly produced by the sudden obstruction to flow in the pulmonary arteries (Scherf and Schonbrunner, 1937, Eckhardt, 1938), has not been confirmed (Megibow et al , 1942; Malinow et al., 1946; Hackel et al , 1954) On the other hand, a *pulmonopulmonary reflex*, in which pulmonary emboli are accompanied by a reflex vasoconstriction of other branches of the pulmonary arteries without intraluminal obstruction, has been demonstrated experimentally and has been discussed above.

HYPOXEMIA Hypoxemia in acute cor pulmonale results from a combination of causes While the existence of *precapillary shunts* between the pulmonary arteries and pulmonary veins has been recognized for some time (Tobin and Zariquiey, 1953), their possible importance in causing hypoxemia very early after pulmonary embolism has been evaluated only subsequently. Niden and Aviado have demonstrated experimentally that the passage of large glass beads (420 μ in diameter) through these shunts was facilitated by increasing pulmonary arterial perfusion pressure, and was hindered by ventilation with 100 per cent oxygen. This marked lability of the pulmonary shunts suggests that pulmonary embolism, by increasing pressure in the pulmonary arterial tree, opens them, thus aggravating the concomitant hypoxemia and at the same time minimizing the rise in pulmonary artery pressure. The hypoxemia, which is aggravated by these shunts, also acts to keep them open. Diminished oxygenation of the blood may also occur as a result of a reduction in pulmonary blood flow. The peripheral circulatory collapse described earlier favors *stagnant hypoxia* in the peripheral tissues.

Despite certain theoretical considerations, *pulmonary edema* has been reported in acute cor pulmonale. This may result from the peripheral circulatory collapse which may follow acute cor pulmonale, since pulmonary edema has been observed in dogs following acute peripheral blood loss and shock (Eaton, 1947). However, there is also evidence that reflex pulmonary venoconstriction contributes not only to the elevation of pulmonary resistance as described above but also to the production of pulmonary edema (Laurent et al, 1956, Niden and Aviado, 1956). Pulmonary edema will interfere with the diffusion of oxygen across the alveolar-capillary barrier and thus will contribute to the hypoxemia (see Part 18, Chaps. 12 and 13)

A *pulmonobronchomotor reflex* causing bronchospasm has been described following embolization. However, experimental methods for measuring bronchomotor tone are likely to record blood volume changes in the lungs, so that true bronchomotor responses are difficult to distinguish from vascular changes (Barer and Nusser, 1953). However, if bronchoconstriction occurs, it would contribute to the hypoxemia, as well as tend to increase resistance to blood flow through the lungs. The dyspnea and tachypnea occurring in pulmonary embolism are well recognized The changes in respiratory frequency and depth which occur after pulmonary embolism are complex and result from many influences and reflexes. *Hypoxemia*, if present, contributes to the reflex production of tachypnea, but tachypnea occurs even in the absence of hypoxemia, or if the hypoxemia is corrected (Megibow et al., 1942 and 1943; Whitteridge, 1950; Niden and Aviado, 1956). However, there is no good evidence that inefficient ventilation contributes to the hypoxemia.

precordium. When inversion is limited to lead V_2, it may be due to extreme clockwise rotation of the heart. When the T-wave inversion extends to leads V_3 and V_4, it may be a reflection of myocardial ischemia or of the poorly understood phenomenon of acute right ventricular strain. Contrary to the pattern in anterior-wall infarction, abnormal elevation of the S-T segments in the precordial leads usually does not occur, except occasionally in leads V_1 and V_2

c Development of a Q wave with inversion of the T wave in lead III Contrary to earlier reports in acute cor pulmonale, a small Q wave is either present (vertical position of heart) or absent (semihorizontal position of heart) in lead aVF. In the latter case, the Q_3T_3 pattern is related to the fact that the R and T waves are taller in aVL than in aVF. Lead III, which is roughly equivalent to (aVF − aVL) × ⅔, will as a consequence show a Q wave and an inverted T wave (Myers and Oren, 1945). Whether the reduction in amplitude of R and T waves in aVF is partially due to severe ischemia of the diaphragmatic surface of the heart, or is merely a result of changes in the heart's position is not known at this time Contrary to the usual pattern in posterior-wall myocardial infarction, *a Q wave and an inverted T wave are usually not present in lead II* The vectorcardiogram further aids in differentiating acute cor pulmonale from posterior-wall myocardial infarction.

d Development of so-called *incomplete or even complete right bundle branch block* with a late R' in the leads from the right precordium This may appear early or late after the onset of acute cor pulmonale, it may be transient or permanent (Durant et al, 1939) This apparent conduction defect in the right ventricle may be due to the mechanical effect of the sudden marked dilatation of the right ventricle and the ischemia of the right ventricular myocardium

e Development of a *P pulmonale* (tall P wave in leads II and III, sharply diphasic P wave in V_1 to V_2)

f Sinus tachycardia is almost always present. *Arrhythmias* of almost any type

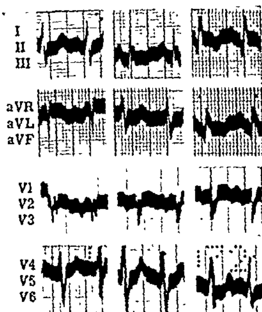


Fig. 13-26. Acute cor pulmonale due to massive pulmonary embolism 10 days after cholecystectomy in a 50-year-old female patient. Sinus rhythm. S waves are present in leads I, aVL, and V_6. S-T depression of the "staircase variety" is present in leads I, aVL, V_5, and V_6. Q and inverted T waves are present in leads III and aVF. R wave is very small in leads V_2 and V_3 T wave is inverted in leads II and III. The transitional zone over the precordium is shifted to the left Discussed in text.

are very frequent. They may be produced reflexly, and hence are neurogenic in origin. They may also be due to ischemia of the myocardium leading to areas which act as ectopic foci for the origin of ectopic rhythms, or to areas in which conduction is critically slowed to permit the development of reentry mechanisms, which then are responsible for the arrhythmias (Katz and Pick, 1956, Mack and Langendorf, 1950) The development of a *P pulmonale* is usually a grave prognostic sign (Eliazer and Giansiracusa, 1952).

The changes described may appear several hours after the episode, and usually disappear after 4 to 10 days. Persistence of the pattern may speak for repeated small pulmonary embolizations (Phillips and Levine, 1950). The evolution is not prolonged over a period of 6 to 10 weeks, as in myocardial infarction.

The above listing of the changes occurring in acute cor pulmonale is intended to include all the classic changes. It was formerly believed

right ventricular dilatation and failure, cyanosis, fever, and sudden death.

Evidences of pulmonary infarction include pleuritic chest pain with or without a friction rub, pleural effusion (often hemorrhagic), marked local chest tenderness, hemoptysis, cough, dyspnea, and tachycardia (Parker and Smith, 1958).

While *hemoptysis* and a *friction rub* have been considered the classical signs of pulmonary embolism, they are not the most common. More frequent are such nonspecific symptoms as *fever, tachycardia, pleuritic chest pain*, and *dyspnea*. Any combination of all the above symptoms and signs may be present and may mimic acute pulmonary or cardiac disease

Myocardial infarction is frequently complicated by pulmonary embolism, but pulmonary embolism may also precipitate *subendocardial myocardial infarction*, especially in a patient with coronary sclerosis. Severe *diaphragmatic pleuritis*, associated with a basal pulmonary infarct, may simulate an acute abdominal condition.

Although most emboli originate in the veins of the legs, objective evidence of *phlebitis* is present in only about 50 per cent of cases (Israel and Goldstein, 1957)

A polymorphonuclear leucocytosis and elevation of the sedimentation rate occur often Significant elevation of the serum glutamic oxalacetic transaminase level occurs only *rarely* in the absence of hepatic dysfunction, myocardial infarction, extensive lung necrosis, or muscle injuries (Goldstein et al , 1956) When elevation of transaminase levels does occur in pulmonary infarction, the values are usually lower than with myocardial infarction, and the elevation occurs relatively late (24 hr after the myocardial infarction, and 3 to 6 days after the pulmonary embolism). This determination is, therefore, frequently of value in differentiating the two conditions (Agress et al , 1956, Ostrow et al., 1956). Hyperbilirubinemia and (rarely) clinical jaundice have occasionally been observed. While, in the past, this has been attributed to hemolysis in the infarct, it is generally agreed that it is usually due to hepatic dysfunction, preexisting or due to congestion or hypotension.

ROENTGENOLOGY

The diagnosis of pulmonary embolism or infarction cannot be made from the roentgenogram alone. The x-ray may show no abnormalities, even after repeated embolizations. Occasionally, a film may show relative avascularity of the area of the lung distal to the embolus (Westermark, 1938).

If acute cor pulmonale has developed, dilatation of the main pulmonary artery and its major branches may be apparent. Usually, however, the changes in the x-ray are a result of pulmonary infarction. The infarcts are often multiple, usually appear at the bases of the lung, and are often contiguous with the pleural surfaces.

The classical wedge-shaped density with apex directed to the hilum is not usually observed; pulmonary infarcts may present any shape on x-ray, resembling patches of pneumonitis or subsegmental atelectasis. *Pleural effusion* is common, often with elevation of the hemidiaphragm; this may obscure the infarct itself. Serial films show the shadows to clear usually by contraction into linear or stellate densities, rather than by resolution. This type of evolution may help suggest the diagnosis.

ELECTROCARDIOGRAPHIC CHANGES

The electrocardiographic features of acute cor pulmonale (Fig. 13-26) may be correlated with the two main dynamic alterations which occur.

1 The development of *sudden dilatation of the right ventricle* leads to a change in position of the entire heart: clockwise rotation about its longitudinal axis, as well as the assumption of a more vertical position (McGinn and White, 1935; Wilson et al., 1947). This change in position is responsible for the appearance of deep S waves in leads I and II It also causes a shift of the transitional zone to the left in the precordial leads (Mack et al., 1950a, Weinschel et al , 1951, Eliaser and Giansiracusa, 1952)

2 The electrocardiographic changes that follow may be considered to be a reflection of *myocardial ischemia*, particularly of the right ventricle and posterior wall of the left ventricle

a. Depression of the S-T junction and segment in leads I, II, aVL, V_5, and V_6, of a type described by McGinn and White as being of the "staircase" variety.

b Inversion of the T wave in the precordial leads from the [illegible] half of the

THE CAUSES OF CHRONIC COR PULMONALE

Chronic cor pulmonale develops when the involvement (structural or functional) of the lungs or its vessels is bilateral and *diffuse*, and not *unilateral or focal* Classifications in the past have usually been based on the anatomic location of the pulmonary disease process. More useful is a classification which correlates *anatomic and functional abnormalities* and, in addition, has important therapeutic implications According to this classification, the etiology of chronic cor pulmonale may be divided into *three main groups*: type I–pulmonary diseases and dysfunction associated with chronic diffuse obstructive emphysema, type II–pulmonary diseases and dysfunction with *chronic alveolar hypoventilation*; and type III–pulmonary diseases in which the pathologic process and dysfunction are localized in or about the pulmonary vessels (see Classification of Causes of Chronic Cor Pulmonale). This classification is not rigidly exclusive, for some cases may demonstrate features of more than one type of pulmonary involvement. Therapy is usually much more satisfactory in chronic cor pulmonale of types I and II than in type III. This is so because at least some of the structural and functional abnormalities which cause the development of chronic cor pulmonale in these types are partially reversible (Mack and Snider, 1953) This reversibility will be regularly noted in the discussion to follow

In patients with chronic pulmonary disease having a markedly restricted pulmonary vascular bed, the abrupt development of some pulmonary catastrophe, such as extensive pneumonitis or massive collapse of a lung, which produces a critical increase in pulmonary vascular resistance, may cause a rapid dilatation of the right ventricle associated with myocardial ischemia and death The clinical picture, the electrocardiographic changes, and the pathologic findings will be similar to those of acute cor pulmonale, although no pulmonary embolization has occurred (Mack et al, 1950)

Classification of Causes of Chronic Cor Pulmonale

I Pulmonary disease with predominant chronic diffuse obstructive emphysema
   A Chronic bronchitis and idiopathic chronic diffuse obstructive emphysema
   B. Bronchial asthma
   C. Chronic pulmonary tuberculosis
   D Sarcoidosis

II.

center
involve-

III

ry
embolism
   2. Thrombosis of major pulmonary arteries
   3 Sickle-cell anemia

occlusion
   B. Extraluminal processes
      1. Sarcoidosis
      2. Beryllium disease
      3. Histiocytosis X
      4. Hematogenous tuberculosis
      5. Wegener's granulomatosis
      6. Pneumonoconiosis

by
ry
veins
12.
13.
14
the lung
      15. Extrinsic compression of main pulmonary arteries
IV. Combinations of types I through III

TYPE I: PULMONARY DISEASE WITH PREDOMINANT CHRONIC DIFFUSE OBSTRUCTIVE EMPHYSEMA

In the United States, *chronic diffuse obstructive emphysema* is by far the commonest cause of chronic cor pulmonale While there is considerable controversy about the pathogenesis of this process, there is little argument about the functional abnormalities

Chronic diffuse obstructive emphysema is associated with an absolute increase in the residual volume and functional residual capacity. There is a decrease in the vital capacity and maximum breathing capacity, the decrease of the latter being more marked. The work of breathing is greatly increased (Mc Ilroy and

that recognizable electrocardiographic changes could be found in only 10 per cent of cases of acute cor pulmonale. With the use of multiple leads, some changes which would make one suspect the presence of acute cor pulmonale are seen to occur in the majority of cases. However, only by understanding the physiologic mechanisms underlying the electrocardiographic changes can one recognize and understand the electrocardiographic picture when it presents itself in a less typical fashion.

TREATMENT

Prevention of thromboembolism has not been very successful. Early ambulation after surgical procedures has not produced a striking reduction in the incidence of thromboembolic phenomena. The application of elastic stockings to the legs of all immobilized hospital patients over the age of 20 has been of definite value (Wilkins and Stanton, 1953). The early recognition of pulmonary embolization, or phlebitis in the legs, is of paramount importance. Once thromboembolic complications have been recognized, the use of *anticoagulant therapy,* while not a perfect preventative, will greatly reduce the frequency of recurrent emboli. *Superficial femoral vein ligation* has been somewhat disappointing. *Ligation of the inferior vena cava* is frequently followed by venous insufficiency of the lower extremities. However, when anticoagulants cannot be employed, or when the discharge of emboli continues despite anticoagulants, the appropriate veins should be ligated. The shock in acute cor pulmonale is best treated by *intravenous levarterenol.* Intravenous *atropine* in high doses has been advocated to block some of the lethal reflexes but has not proved to be of striking value. Pulmonary arteriotomy with *embolectomy* has been tried, but it requires the differentiation of large emboli in the major pulmonary arteries from multiple small emboli. *Oxygen* in high concentration, and *opiates* for pain, should be administered. *Antibiotics* should be given when there is evidence of pulmonary infarction.

CHRONIC COR PULMONALE

Chronic cor pulmonale may be defined as right ventricular hypertrophy resulting from *disordered structure or function* of the lung, the pulmonary circulation, or both. Thus definition excludes such causes of right ventricular hypertrophy as left ventricular failure, constrictive pericarditis, congenital heart disease, and acquired valvular heart disease. The term "pulmonary hypertensive heart disease" has been used to include not only those conditions which fall within the strict definition of chronic cor pulmonale but also all conditions associated with pulmonary hypertension and right ventricular hypertrophy, including left ventricular failure, mitral stenosis, and various types of congenital heart disease with left-to-right shunt. The more narrow definition of chronic cor pulmonale is probably more useful and will be used in the discussion below.

The term "Ayerza's disease" was used by Arrillaga to describe a group of cases similar to one presented by Ayerza in 1901. These were cases in which right heart failure was associated with severe cyanosis, polycythemia (*cardiacos negros*), and pulmonary disease, which Arrillaga presumed was syphilitic in origin. The ambiguity of the term has been attested by the diverse meanings given it in the literature. It has been used to describe a variety of conditions, including everything from chronic cor pulmonale due to chronic obstructive emphysema with cyanosis and secondary pulmonary arteriosclerosis, to primary pulmonary hypertension. It would be best if it could be dropped from usage.

The true incidence of chronic cor pulmonale is higher not only than that given in clinical reports but also than that reported in necropsy series. The cachexia of chronic pulmonary disease is often associated with some degree of *atrophy of the entire heart,* so that relative hypertrophy of the right ventricle is frequently overlooked. With the employment of techniques in which a ratio of left/right ventricular weight, or of left ventricular and septum/right ventricular weight, is obtained, a higher necropsy incidence of chronic cor pulmonale is being reported (Thomas, 1951; Fulton et al., 1952; Wells, 1954b). There will probably be a great increase in the future incidence of chronic cor pulmonale, mainly because better therapy has permitted longer survival of patients with chronic pulmonary disease, particularly pulmonary tuberculosis. Healing often results in pulmonary fibrosis.

THE CAUSES OF CHRONIC COR PULMONALE

Chronic cor pulmonale develops when the involvement (structural or functional) of the lungs or its vessels is bilateral and diffuse, and not unilateral or focal. Classifications in the past have usually been based on the anatomic location of the pulmonary disease process More useful is a classification which correlates anatomic and functional abnormalities and, in addition, has important therapeutic implications According to this classification, the etiology of chronic cor pulmonale may be divided into three main groups. type I—pulmonary diseases and dysfunction associated with chronic diffuse obstructive emphysema; type II—pulmonary diseases and dysfunction with chronic alveolar hypoventilation; and type III—pulmonary diseases in which the pathologic process and dysfunction are localized in or about the pulmonary vessels (see Classification of Causes of Chronic Cor Pulmonale) This classification is not rigidly exclusive, for some cases may demonstrate features of more than one type of pulmonary involvement Therapy is usually much more satisfactory in chronic cor pulmonale of types I and II than in type III This is so because at least some of the structural and functional abnormalities which cause the development of chronic cor pulmonale in these types are partially reversible (Mack and Snider, 1953) This reversibility will be regularly noted in the discussion to follow

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  C. Chronic pulmonary tuberculosis
  D. Sarcoidosis
  E. Kyphoscoliosis
  F. Pneumonoconiosis
  G. Fibrocystic disease of the pancreas
II. Chronic alveolar hypoventilation syndromes
  A. Defective chest bellows
    1. Massive bilateral pleural thickening
    2. Chronic neuromuscular disorders
    3 Kyphoscoliosis
    4 Pickwickian syndrome
  B Disease of the medullary respiratory center
III Pulmonary disease with predominant involvement of the vessels
  A. Intraluminal processes
    1 Multiple recurrent small pulmonary emboli
    2 Thrombosis of major pulmonary arteries
    3. Sickle-cell anemia
    4 Schistosomiasis
    5 Primary pulmonary hypertension
    6 Diffuse pulmonary vasculitis
    7 Other causes of diffuse intravascular occlusion
  B. Extraluminal processes
    1 Sarcoidosis
    2. Beryllium disease
    3 Histiocytosis X
    4 Hematogenous tuberculosis
    5 Wegener's granulomatosis
    6. Pneumonoconiosis
    7 [illegible]
    8 [illegible]
    9 [illegible]
    10 [illegible]
    11 [illegible] by chronic obstruction of the pulmonary veins
    12. [illegible]
    13 [illegible]
    14. [illegible] the lung
    15 Extrinsic compression of main pulmonary arteries
IV Combinations of types I through III

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Chronic diffuse obstructive emphysema is associated with an absolute increase in the residual volume and functional residual capacity There is a decrease in the vital capacity and maximum breathing capacity, the decrease of the latter being more marked. The work of breathing is greatly increased (McIlroy and

Christie, 1954). The larger functional residual capacity, coupled with a widespread but irregular loss of pulmonary elasticity and bronchiolar obstruction, results in a marked impairment of the distribution of inspired air to mixed venous blood (defective intrapulmonary mixing). As the disease progresses, hyperventilation may cause a decrease of the partial pressure of carbon dioxide in arterial blood during exercise without significant hypoxemia. At a later stage, especially with superimposed infection, *hypoxemia* occurs. Eventually, hyperventilation becomes inadequate and *hypercapnia* results. Finally, the respiratory center becomes insensitive to carbon dioxide. Under these circumstances, the main stimulus to respiration is hypoxemia acting on the aortic and carotid chemoreceptors (Baldwin et al, 1949).

Chronic Bronchitis and the Idiopathic Types of Chronic Obstructive Emphysema. In most cases, chronic bronchitis, sometimes but not always associated with bronchiectasis, appears to be the main cause of this type of emphysema (Baldwin et al., 1949, Spain and Kaufman, 1953; Donald, 1953) Most patients with chronic diffuse obstructive emphysema of the so-called idiopathic type thus give a history of repeated lower respiratory tract infections, with chronic cough and expectoration of many years' duration In such cases, it is quite certain that the chronic bronchial and bronchiolar infection with obstruction has been primary in the genesis of the disease, the loss of pulmonary elasticity being secondary Occasionally, however, patients with diffuse obstructive emphysema are encountered in whom such a sequence has not occurred In such instances, the clinical and functional picture of chronic diffuse obstructive emphysema develops rather suddenly, without a long history of chronic cough. There is evidence that in these patients, some poorly understood degeneration of the pulmonary elastic tissue precedes the diffuse airway obstruction It has been suggested that this represents a *degenerative disease of the elastic tissue of the lung*, possibly secondary to obliterative disease of the bronchial arteries (Cudkowicz and Armstrong, 1953; Lilienthal and Riley, 1954). Once the elastic tissue has become disrupted, bronchiolar obstruction does occur on expiration, bronchial cleansing is impaired, and eventually the picture of chronic bronchial infection becomes manifest. Thus, the end stages of these two quite dissimilar pathogenetic mechanisms become almost identical. At present, the implications for treatment are identical, regardless of the origin of the process, since therapy is mainly directed against the diffuse airway obstruction and infection Chronic diffuse obstructive emphysema occurs more frequently in males, in industrial urban centers, particularly in the North Temperate regions, and in mining regions There is no complete agreement that it is more common among those who do heavy labor and among heavy smokers; some feel that atmospheric pollution is more important (Fulton, 1953, Flint, 1954; Lowell et al, 1956).

Bronchial Asthma. Bronchial asthma produces chronic cor pulmonale only if it is severe, of long standing, associated with recurrent infectious bronchitis, and has led to the development of severe diffuse obstructive emphysema. Acute transitory pulmonary arterial hypertension has been demonstrated by cardiac catheterization during *status asthmaticus*

Chronic Pulmonary Tuberculosis. Chronic cor pulmonale develops in chronic pulmonary tuberculosis, usually when there is a complicating severe diffuse obstructive emphysema In such cases, the diffuse obstructive emphysema is a consequence of healed endobronchial tuberculosis and recurrent nonspecific chronic bronchitis and bronchiolitis. Further compromise of ventilatory function and pulmonary circulation often results from extensive destruction or distortion of pulmonary parenchyma; this occurs with scarring, permanent collapse therapy, extensive pleural fibrosis, extirpative surgery, and massive pulmonary artery thrombosis

Sarcoidosis. Sarcoidosis causes chronic cor pulmonale only when the pulmonary involvement is diffuse and severe. This involvement may be of two types In the first type, the granulomatous infiltration is predominantly *peribronchiolar and endobronchial*, resulting in diffuse bronchiolar obstruction and severe diffuse obstructive emphysema. In the second type, the granulomas are located predominantly *interstitially* compressing arterioles, and *in the interalveolar septa* compressing the capillaries, as well as thickening the alveolar capillary membrane (Austrian et al., 1951) This latter type will be discussed in greater detail in the third large category of the causes of chronic

cor pulmonale In most cases of diffuse pulmonary sarcoidosis, both types of changes are present, however, not infrequently, one or the other type of involvement predominates Chronic diffuse emphysema in sarcoidosis has two distinct features not observed in the common obstructive type of emphysema. (1) a greater degree of hyperventilation, which sometimes minimizes the effect of poor gas distribution upon the index of interpulmonary mixing, (2) a lesser disturbance of intrapulmonary gas mixing (Coates and Comroe, 1951; Mc Clement et al, 1951) Diffuse pulmonary *sarcoidosis*, like all diffuse infiltrative processes in the lung, often goes on to the development of multiple small cystic areas and bullae (*honeycomb lung*), and is frequently complicated by spontaneous pneumothorax Pleural complications resulting from this development may further impair pulmonary function, if indeed the pneumothorax does not cause acute cor pulmonale and death (Mack et al., 1950) Sarcoid infiltration of the myocardium may be present, and may cause AV block and sudden death A left heart "strain" pattern has been reported in myocardial *sarcoidosis* (Peacock et al, 1957). Where *sarcoid* involves mainly the hilar nodes, chronic cor pulmonale does not develop However, even in such cases, considerable parenchymal infiltration may be present, the roentgenogram often being deceptively clear

Kyphoscoliosis. Chronic cor pulmonale frequently develops in severe kyphoscoliosis. While the major abnormality is *alveolar hypoventilation* due to anatomic restriction of the chest bellows (to be amplified below), these patients suffer from *recurrent bronchopulmonary infections*, which are often perpetuated by interference with bronchial cleansing and a poor tussive mechanism In such cases, diffuse airway obstruction, defective intrapulmonary mixing, and all the functional and structural abnormalities of obstructive emphysema combine with the restriction of the chest bellows to lead to chronic cor pulmonale (Mack and Snider, 1956, Gray, 1956, Snider et al, 1958)

Pneumonoconiosis Many of the pneumonoconioses may be associated with severe diffuse obstructive emphysema, and chronic cor pulmonale may result This includes silicosis, coal miners' pneumonoconiosis (anthrosilicosis), bauxite pneumonoconiosis (Shaver's disease), and diatomite pneumonoconiosis (Vorwald, 1957).

Fibrocystic Disease of the Pancreas. In fibrocystic disease of the pancreas (mucoviscidosis), the production of an abnormal viscid secretion in the bronchial glands leads to diffuse bronchial and bronchiolar obstruction and recurrent bronchopulmonary infection Diffuse obstructive emphysema develops, and chronic cor pulmonale is a frequent finding in advanced cases (di Sant' Agnese).

Pathologic Physiology of Type I Chronic Cor Pulmonale. Hypertrophy of the right ventricle develops in chronic diffuse obstructive emphysema because of its increased work. The reversibility of those elements which cause the right heart strain will be *stressed, since when* therapy is attempted, it is this very *element* of *reversibility* which offers hope of improvement (Mack and Snider, 1956). This increased load on the right ventricle is a result of increased resistance to pulmonary blood flow and, when present, of increased cardiac output.

INCREASED RESISTANCE TO PULMONARY BLOOD FLOW Increased resistance to the flow of blood through the lungs in chronic obstructive emphysema results from (1) a *reduction in* the cross-sectional diameter and the distensibility of the pulmonary vascular bed; (2) increased viscosity of the blood (if polycythemia has developed), and (3) possibly certain functional consequences of an expansion of intrapulmonary vascular shunts

Reduction in Cross-sectional Diameter and Distensibility of the Pulmonary Vascular Bed. The evolution of the complicated circulatory system present in higher vertebrates, by producing a complete division of the primitive ventricle into two chambers, not only resulted in the separation of arterial from venous blood but also provided conditions in which the systemic pressure could be raised without directly affecting the pulmonary blood pressure and blood flow Thus, in man, as well as in all higher vertebrates, while the systemic arterial circulation is a high-pressure system, the pulmonary circulation operates under low pressure with a low resistance to blood flow. This low resistance is a result of the large caliber and the marked distensibility of the pulmonary vascular bed The pulmonary capillaries lack tissue support and are exposed over nearly their entire surface to their environment. The fact that only a small increment in pressure occurs with a greatly increased volume of blood flow is of great

adaptive significance, since a markedly increased pressure in such a capillary bed would produce a transudate and would disturb respiratory function (Rodbard et al., 1949; Rodbard, 1953). In normal man in the upright position, pressure in the pulmonary artery remains unchanged, even when the cardiac output is doubled (Hickman and Cargill, 1948). Even with severe exercise, only slight increases in pressure in the pulmonary artery occur (Freedman et al., 1955). Thus, pulmonary blood flow may increase markedly with only an increase in the velocity of flow and in the caliber of the pulmonary vascular bed, but with little or no increase in pulmonary artery pressure. This enlargement of the pulmonary vascular bed results not only from the distention of the individual vessels but also from the opening of vessels formerly not functioning for flow The distensibility of the pulmonary vascular bed may be lowered by a reduction in the total number of vessels in the lung (since each vessel contributes its increment of distention), by a reduction in caliber of the vessels, and by an increase in rigidity of the individual vessel walls (Mack and Snider, 1956)

Contributing to the reduction in cross-sectional diameter and distensibility of the pulmonary vascular bed in chronic obstructive emphysema are the following pathologic changes·

1. *Conversion of many small air spaces into fewer larger air spaces and bullae* by the rupture of interalveolar septa involves a true loss of capillary bed. In addition, many of the vessels adjacent to the bullae are compressed. Because of the dependence of air entrapment on bronchial and bronchiolar obstruction, treatment may reduce the size of bullae.

2. *Shrinkage of the vascular bed in the lungs* occurs also in areas of necrosis with replacement by relatively avascular scar tissue, which is frequently supplied by blood from the bronchial rather than the pulmonary arteries.

3 *Vascular narrowing and diminished distensibility* may also result from the following Actual compression of the capillary bed occurs in the scattered areas of alveolar exudate, atelectasis, and entrapment of air, this is reversible Periarteriolar inflammatory exudate and fibrosis will also produce narrowing. Actual thrombosis develops in many of the capillaries, arterioles, and small pulmonary arteries. Resolution and recanalization may partially reverse these changes Vascular changes secondary to increased intravascular pressure also contribute to the reduction in the vascular bed. They include endarteritis obliterans, medial hypertrophy, pulmonary atherosclerosis, and occasionally necrotizing arteriolitis. These changes increase resistance to blood flow and, hence, pulmonary vascular pressure, the latter furthers the secondary hypertensive vascular morphologic changes. A vicious cycle thus becomes established. Changes in the small vessels are more important than atheromatous changes in the pulmonary arteries, unless the latter lead to thrombosis. It is known from studies in other conditions, in which secondary pulmonary vascular changes occur, such as mitral stenosis and some types of congenital heart disease associated with pulmonary hypertension, that many of these secondary vascular changes (particularly the endarteritis obliterans and the medial hypertrophy) are partially reversible.

4. *Hypoxia produces pulmonary hypertension* (Euler and Liljestrand, 1946), but how it effects this is still a subject of considerable controversy. There is disagreement as to the degree to which the pulmonary circulation reacts passively to changes in cardiac output and shifts in blood volume from the systemic to the pulmonary circulation, and the extent of local and neurohumoral mechanisms which actively alter the resistance to flow and thus control, in some degree, the flow through the pulmonary vascular bed (Lilienthal and Riley, 1954). Some observers have felt that the pulmonary arterioles are not capable of much constriction. However, Burton (1958) has shown that the pulmonary arterioles are capable of contraction He produced casts of the pulmonary arterioles after the administration of rather large amounts of norepinephrine, and demonstrated marked "gnarling" of these vessels, owing to contraction of the helical muscles. Moreover, indirect measurements of the vascular resistance of the lungs based on pressure and flow are often complicated by passive changes in resistance induced by alterations in pulmonary blood flow (Doyle et al, 1952, Williams, 1954, Aviado and Schmidt, 1955) It is agreed that hypoxia causes an increase in cardiac output, which, in the face of an already restricted pulmonary vascular bed, contributes significantly to the pulmonary hypertension However, whether or not hypoxia causes an increase in resistance to blood flow through the lungs is still very much in dispute The subject is further complicated by the fact that various observers have studied this phenomenon in different species of animals under widely varying experimental conditions, and after the production of varying degrees of hypoxia *However, a vast body of convincing experimental evidence indicates that there are local as well as neurohumoral mechanisms which, in response to hypoxia, increase pulmonary resistance by an actual reduction in the caliber of the pulmonary vessels* The site of this vasoconstriction is as yet unknown, various investigators having placed it in the pulmonary arterioles, capillaries, or venules (Nisell, 1950, Hall, 1953, Duke, 1954, Cournand, 1957). Some

mechanism must exist to account for the absence of significant venous admixture appearing in arterial blood during periods of minimal ventilation in normal man, and in diseased states, when ventilation is reduced or abolished in certain areas of the lungs (Lilienthal and Riley, 1954) When chronic hypoxia has led to polycythemia, additional factors increasing resistance to pulmonary blood flow are brought into play and are discussed below. Hypoxia and its effects are reversible.

5 While there has been suggestive experimental evidence that hypercapnia also contributes to an increase in pulmonary arterial pressure, the extent and the mechanism of this effect are as yet imperfectly understood (Nisell, 1950, Shepard, 1954, Lilienthal and Riley, 1954).

Secondary Polycythemia. Secondary polycythemia in chronic obstructive emphysema is caused by hypoxemia. *Hypoxemia stimulates erythropoiesis,* not by a direct effect on the bone marrow, but by increasing the production of a plasma erythropoietic stimulating factor (*erythropoietin*) The site of erythropoietin elaboration is as yet unknown (Erslev, 1953; Stohlman et al, 1954, Reissman, 1955). Secondary pulmonary polycythemia is not associated with marked leucocytosis and thrombocytosis, as is polycythemia vera.

Secondary polycythemia is not invariably present, even in the presence of marked arterial oxygen desaturation It has been suggested that chronic bronchopulmonary infection may be one of the factors causing such failure of the hematopoietic response (Wilson et al, 1951) *Secondary polycythemia is associated with an increased blood viscosity and an increased blood volume, due to an increased red cell mass* The increased viscosity increases the resistance to blood flow in the lungs, but to what extent is unknown Van Liere has shown that an increase of one-third in the proportion of red cells increases the viscosity of the blood three times. However, the viscosimeter measures blood as though it were a homogeneous fluid There is probably an axial flow of red cells in the small arterioles while the plasma moves slowly along the periphery (Brinton, 1951) The effect of viscosity will probably be most marked when the blood flow is at a slow rate and the vessels are reduced in size (Lewis et al., 1952), the conditions prevailing in patients with chronic cor pulmonale and cardiac failure

The increased blood volume in secondary polycythemia is due almost entirely to an increase in red cell mass; *the plasma volume is usually normal,* except in the presence of congestive failure or immediately after recovery from failure. This *hypervolemia* is usually associated with an increased venous return, an increased cardiac output, and probably an increased residual volume of blood in the lung. The latter, in face of an already limited pulmonary vascular capacity, may result in a further encroachment on the ability of the pulmonary vascular bed to accommodate an increased blood flow without an increase in pressure. Increased residual blood in the lungs also decreases pulmonary compliance (Mack et al, 1947), and so would tend to increase the work of breathing. Since satisfactory methods are not available for determining pulmonary residual blood volume, the importance of this factor cannot be evaluated.

Secondary polycythemia in patients with chronic obstructive emphysema is an attempt at compensation, not only because the polycythemia causes an increase in the oxygen capacity of the arterial blood, but because the hypervolemia, by increasing venous return to the heart, helps to increase cardiac output and maintain a high pulmonary blood flow (Guyton et al, 1954, Mack and Snider, 1956). Such indeed occurs in normal people exposed to high altitudes, where the adjustment to hypoxemia includes polycythemia, and often also, increased cardiac output. Some fear that bleeding a polycythemic subject with chronic lung disease may uncover a state of oxygen unsaturation, reflecting the conditions which originally led to the development of the secondary polycythemia (Lewis et al., 1952). However, in a patient with chronic obstructive emphysema, at some point, the deleterious effects of the polycythemia probably outweigh the possible advantages because of the restricted pulmonary vascular bed. Furthermore, Starling demonstrated that a rising filling pressure (venous or right atrial pressure) caused an increase in cardiac output only through a limited range If the filling pressure were increased beyond a certain value, the output would reach a plateau, and if the pressure were raised further (overdistention of heart), the output would begin to decrease Thus, Mc Michael observed that in some patients with chronic cor pulmonale, the cardi-

put usually "fell" on the "normal," or left, side of Starling's curve, so that lowering of venous pressure by venesection led to a decrease in cardiac output. The immediate effect of bleeding in such a case would be undesirable. However, others have studied cases of chronic cor pulmonale in severe congestive failure, when the venous pressure was very high, when cyanosis was extreme, and where the state of the patient's heart "fell" on the right side of Starling's curve (i e, the right ventricle was overdistended). In such cases, phlebotomy (which decreased the venous pressure) remedied the overdistention of the heart, increased cardiac output, and improved the blood flow to the tissues of the body (De Vries et al., 1950) It is possible that in the future, the exact extent to which phlebotomy should be employed in therapy will be determined from correlative studies of viscosity, pulmonary vascular resistance, pulmonary residual blood, total blood volume, and cardiac output. Phlebotomy should be utilized moderately in therapy and only in conjunction with all the other therapeutic procedures available to treat the pulmonary disease

Intrapulmonary Vascular Shunts. While there is no complete agreement about the extent or even the existence of precapillary anastomoses between the bronchial arteries and the pulmonary arteries in the normal lung (Liebow et al., 1949; Tobin and Zariquiey, 1953), their presence and considerable size have been clearly demonstrated in diseased lungs (Liebow et al, 1949). In dogs, following ligation of one pulmonary artery, collateral circulation from the bronchial arteries will expand to such an extent that one-third of the cardiac output will be carried by the bronchial arteries on that side (Bloomer et al, 1949) (see also Chap. 3)

Large and numerous precapillary shunts between the bronchial and pulmonary arteries have been demonstrated in lungs with chronic bronchial infection, tuberculosis, and chronic fibrosing disease by Liebow and associates. They feel that the expansion of these anastomoses in chronic obstructive emphysema is related to their development or enlargement in granulation tissue, in areas of organizing pneumonitis, in the walls of bronchiectatic sacs, and in areas of lymphoid hyperplasia and hypertrophied bronchial smooth muscle They suggest the following consequences of such functioning anastomoses between a high- and low-pressure system. (1) They might act to shunt desaturated pulmonary artery blood away from poorly ventilated areas of the lung, in which they occur to the greatest extent, thus, whatever blood does pass through these poorly ventilated areas would have a higher oxygen content, and less pollution of the systemic blood would then occur (2) They increase the blood flow through the lungs, and in the presence of a restricted vascular bed serve to further elevate pulmonary artery pressure. (3) They tend to increase the work of the left ventricle, since in effect they are a shunt between the left ventricle and left atrium. (4) They may produce an actual reversal of blood flow in the pulmonary artery toward the hilus in some areas; catheterization of patients with extensive bronchiectasis limited to one lung has been shown to yield blood from the pulmonary artery on the affected side that was almost arterial in character (Roosenburg and Deenstra, 1954).

The existence of *anastomoses between the bronchopulmonary veins and the pulmonary veins* has long been recognized (Zuckerkandl, 1882) (see also Chap. 3). The smaller bronchi are drained by the pulmonary veins, while the bronchopulmonary veins drained the proximal two to three orders of branches of the trachea and surrounding interstitial tissue. The bronchopulmonary veins drain into the azygos and hemiazygos systems, the pulmonary veins into the left atrium Normally, blood flow across these anastomotic channels is from the pulmonary veins to the bronchopulmonary veins and thence to the azygos or hemiazygos veins. This is so because the pressure in the left atrium is higher than in the right and because there are valves at the site of entrance of the bronchopulmonary veins into the azygos and hemiazygos veins which ensure unidirectional flow The value of these anastomoses is seen where suppuration exists in the lungs, causing thrombosis of pulmonary veins. In such cases, blood is drained away from the area by the bronchopulmonary veins (Liebow, 1953).

In chronic obstructive emphysema, great expansion in the extent and size of these anastomotic venous channels has been demonstrated. The causes of this expansion are incompletely understood Liebow has suggested that changes in the respiratory pumping action in chronic obstructive emphysema, which affect the true pulmonary venules to a greater extent than the more protected bronchopulmonary venules, might favor this expansion Bullae have been shown to represent expanded parts of the respiratory tract more proximal than alveoli, and the venous drainage of these structures is by way of the bronchopulmonary veins rather than by the pulmonary veins, just as their arterial supply comes from the bronchial arteries. Also, it has been shown that the

walls of bullae contain granulation tissue and much smooth muscle. During the formation of granulation tissue, these anastomotic channels form and persist, even after resolution or cicatrization

In chronic obstructive emphysema, an actual reversal of flow in these expanded channels may occur, so that blood would flow from the bronchopulmonary veins to the pulmonary veins. This might occur, particularly in chronic cor pulmonale with right heart failure, where the pressure in the azygos-hemiazygos system will exceed that in the pulmonary veins In addition, dilatation of the bronchopulmonary veins will cause the stretching of the valve rings at their connections with the azygos or hemiazygos veins, producing incompetence of these valves Such reversal of blood flow would tend to cause pollution of systemic arterial blood by desaturated hypercapnic venous blood, and could thus furnish an important proportion of the venous admixture in the arterial blood

This expansion of the bronchial arterial and bronchopulmonary venous systems, clearly demonstrated in chronic obstructive emphysema, has been quantitatively evaluated (see Chap 3) Evidence for their existence should stimulate the development of methods for assessment during exercise and during respiratory infections

The presence of *precapillary anastomoses* between pulmonary arteries and pulmonary veins has been demonstrated in normal man, but it is apparently not extensive enough to be significant under ordinary circumstances (Tobin and Zariquiey, 1950)

Perfusion of poorly ventilated parts of the lung is equivalent in effect to shunting blood from the pulmonary arterial to the pulmonary venous system However, in chronic pulmonary disease, this phenomenon is minimized (Wilson et al, 1951), since blood flow through these areas usually is reduced markedly by all the mechanisms described as causing an increased resistance to blood flow

CARDIAC OUTPUT. The divergence in the reported studies of cardiac output in chronic cor pulmonale due to chronic obstructive emphysema (Dexter et al, 1951, Harvey et al, 1951, Taquini and Gonzalez, 1951, Fowler et al, 1952, Whitaker, 1954) is explained by the fact that the cardiac output at any particular time in these patients depends on a complex interplay of many variables—not only on the type and extent of pulmonary disease present, but also on the stage of the disease in which the patient is being studied—and will be profoundly affected by the presence of acute bronchitis or pneumonitis, the degree of hypoxia, the severity of polycythemia, the blood volume, and, very importantly, the presence and degree of heart failure.

An increased cardiac output, especially in the face of heightened pulmonary vascular resistance, greatly increases the work of the right ventricle. The following mechanisms act to increase cardiac output in chronic cor pulmonale. Exercise increases cardiac output; even a mild increase in cardiac output through a restricted pulmonary vascular bed causes a disproportionate increase in work of the right ventricle. *Hypoxia acts directly to increase cardiac output If polycythemia is present, the associated hypervolemia will also contribute to an increased cardiac output.* Activity of the inflammatory process in the lung, since some degree of bronchopulmonary infection is always present even in the absence of fever, tends to increase oxygen consumption of the body and thereby lead to an increase in cardiac output. The increased muscular work of breathing, shown to be present in chronic obstructive emphysema, also disposes to an increased cardiac output (Mc Ilroy and Christie, 1954; Otis, 1954) Should cardiac failure occur at a stage when the cardiac output is elevated, some drop in cardiac output will occur, but the output may still be higher than normal The paradox of "high-output failure" is thus explained by the magnitude of the output just preceding failure of the right ventricle (Harvey et al, 1951, Katz, 1954).

When congestive heart failure develops, the increased plasma volume which so often accompanies congestive failure also helps to maintain the cardiac output (Guyton et al, 1954, Starling, 1918), however, later, by contributing to the overdistention of the right ventricle, it may help to lower it.

All these factors which act to increase cardiac output are potentially reversible by intense treatment; a patient who has a high cardiac output during a desperate stage of his illness may have a normal output after a successful course of treatment. If the above factors, which tend to produce an increased cardiac output, are less marked in extent or of shorter duration, a normal cardiac output may be observed

A *lower-than-normal cardiac output* may appear in chronic cor pulmonale due to chronic obstructive emphysema under various circum-

stances. Most important is the effect of severe cardiac failure in causing a marked lowering of cardiac output. If the factors tending to produce high cardiac output are present but pulmonary vascular resistance is high (over four times normal), cardiac output will be low (Dexter et al., 1951). In such instances, the markedly restricted vascular bed of the lung acts very much like a "tight mitral stenosis" in limiting pulmonary blood flow and hence cardiac output. This marked increase in pulmonary vascular resistance may be due to the severe anatomic changes in the lungs associated with the chronic obstructive emphysema, as described above, or it may be due to a coexisting disease, such as multiple pulmonary emboli (Harvey et al., 1951).

In chronic cor pulmonale with congestive failure, the administration of *digoxin* intravenously may cause a paradoxical rise in pulmonary artery pressure. This can be explained by the fact that digoxin causes an increase in cardiac output and probably better emptying of the failing right ventricle. The resultant increased blood flow through a pulmonary vascular bed which is reduced in size and in distensibility causes a rise in pulmonary artery pressure. Acute digitalization in patients with cardiac failure with chronic pulmonary disease and pulmonary hypertension, but with arteriosclerotic or hypertensive heart disease, causes a drop in pulmonary artery pressure This, thus, differentiates pulmonary hypertension due to a reduction in the pulmonary vascular bed from that due to left ventricular failure (Ferrer et al., 1950)

While these patients have pulmonary arterial hypertension, their pulmonary arterial wedge pressure is normal This differentiates the pulmonary hypertension present in chronic obstructive emphysema from that which may be present in patients with mitral stenosis or left ventricular failure, where both the pulmonary arterial wedge and the pulmonary arterial pressures are elevated (Dexter et al, 1951). Often, in a patient with chronic cor pulmonale in congestive failure with marked pulmonary hypertension and increased cardiac output, repeat catheterization after intense pulmonary and cardiac therapy will show the cardiac output to be normal, and the pulmonary artery pressures normal or nearly normal at rest, becoming elevated only with exercise (Harvey et al., 1951).

Since intensive treatment of bronchopulmonary disease increases the size of the pulmonary vascular bed, as well as reducing or abolishing hypoxia with its circulatory effects, it is difficult in any specific case to know which abnormality is responsible for the precipitation of right heart failure. While some observers feel that hypoxia is the main culprit, it is quite likely that the relative importance of each factor varies from case to case, and that, in some cases, therapy is effective mainly because it actually reduces the extent of anatomic restriction of the pulmonary vascular bed by partially reversing the pathologic processes described above (Mack and Snider, 1956).

TYPE II: CHRONIC ALVEOLAR HYPOVENTILATION SYNDROMES

This category includes disorders in which the important functional abnormality is *alveolar hypoventilation*, which, when of sufficient severity and duration, leads to hypoxemia, hypercapnia, polycythemia, pulmonary hypertension, right ventricular hypertrophy, and failure. This category may be subdivided into two groupings: (1) conditions associated with poor functioning of the chest bellows, and (2) primary disease (insensitivity) of the respiratory center (see classification, Causes of Chronic Cor Pulmonale, above). In most of the chronic alveolar hypoventilation syndromes, the respiratory center becomes less sensitive to the carbon dioxide stimulus because of the chronic hypercapnia Further carbon dioxide retention may contribute to a vicious cycle by further depressing respiration and interfering with carbon dioxide excretion (Auchincloss et al, 1955). This loss of sensitivity to the carbon dioxide stimulus is reversed by weight reduction in the cardiopulmonary syndrome associated with obesity. Whether or not it is reversible in the other conditions, is not known, but it is known that it is not reversible in chronic diffuse obstructive emphysema (Baldwin et al, 1955)

Defective Chest Bellows. MASSIVE BILATERAL PLEURAL THICKENING. Encasement of both lungs by a markedly thickened inelastic pleura may restrict the bellows action sufficiently to cause severe alveolar hypoventilation. In some

cases, the chest bellows is further impaired by paralysis of a hemidiaphragm, resulting from a phrenic crush that occurred in the past At necropsy, these patients show no intrinsic disease of the pulmonary parenchyma or of the pulmonary vessels (Feltman et al., 1952, Cabot, Case 43421; Coates et al , 1958).

CHRONIC NEUROMUSCULAR DISORDERS Defective action of the chest bellows due to chronic neuromuscular disorders has been reported to cause chronic cor pulmonale. This has been observed in patients with severe residual respiratory paralysis after poliomyelitis, muscular dystrophies, myasthenia gravis, or amyotrophic lateral sclerosis After poliomyelitis, a primary involvement of the respiratory center by this syndrome is possible, but the part played by this factor is not always easy to evaluate The exact effect of prolonged *existence in a respirator* has also yet to be fully assessed (Lucas and Plum, 1952, Blossom and Affeldt, 1956, Cherniack et al , 1957; Eldridge, 1958)

KYPHOSCOLIOSIS In severe kyphoscoliosis, the development of pulmonary insufficiency and chronic cor pulmonale has been long recognized Only recently, however, have detailed *pulmonary function tests* (measurement of lung volumes, airway obstruction, distribution defect, and diffusion capacity) as well as studies of altered cardiovascular dynamics (right heart catheterization) been available.

In severe kyphoscoliosis, there is restriction of the chest bellows with ventilatory dysfunction reduced lung volumes, lowered vital capacity, and lowered maximum breathing capacity There is an increase in the work and energy cost of breathing, to which a partial adjustment is made by a breathing pattern of small tidal volume and a rapid respiratory rate (Grav, 1956, Fishman et al , 1958) This type of breathing pattern involves a relative increase in dead-space ventilation, at the cost of alveolar ventilation When alveolar hypoventilation is severe enough, *hypoxemia* (with all its unfavorable consequences, described below) and *hypercapnia* develop

There is disagreement among observers as to the presence of other functional abnormalities in these patients. Some feel that the cardiopulmonary abnormalities are due exclusively to *alveolar hypoventilation* resulting from restriction of the chest bellows, with consequent hypoxemia and hypercapnia. The chain of events (hypoxemia, hypercapnia, polycythemia, pulmonary hypertension, and chronic cor pulmonale) is considered to arise mainly as a result of this alveolar hypoventilation (Schaub et al , 1954). Others feel that an *anatomically restricted vascular bed* also contributes to the increased load on the right ventricle, since pulmonary hypertension may be observed in some patients with exercise in the absence of arterial hypoxemia (Fishman et al., 1958). Angiocardiographic studies have shown that no significant kinking of the pulmonary artery occurs.

Some observers feel that airway obstruction, defects in intrapulmonary mixing, and obstructive emphysema are not usually present in kyphoscoliotic patients who have developed chronic cor pulmonale (Fishman et al., 1958). However, other observers and the author have seen and reported cases where diffuse airway obstruction, defects in distribution, and functional and pathologic evidence of diffuse obstructive emphysema were apparent (Fischer and Dolehide, 1954, Mack and Snider, 1956; Gray, 1956).

It is most striking that respiratory and cardiac insufficiency are usually *not present early in life*, but develop only after the passage of time It is during this significant time interval that these patients suffer from acute and chronic, recurrent and lingering bronchopulmonary infections, probably associated with *diffuse bronchiolar obstruction* These infections are perpetuated by interference with [illegible] mecha- [illegible] the re- [illegible] the chest bellows Destructive changes in the lung, with areas of emphysema and *atelectasis*, then become superimposed on the impaired respiratory mechanics Chronic obstructive emphysema thus gradually develops, and the restricted vascular bed plus the usual consequences of alveolar hypoventilation combine with it to *produce chronic cor pulmonale* Most of the kyphoscoliotic patients who develop respiratory insufficiency [illegible]

While some patients with severe kyphoscoliosis develop severe cardiopulmonary insufficiency, others, who superficially appear just as deformed, show very little impairment of function or even reduction in life expectancy. There is a great need for some method for (1) evaluating quantitatively the type and severity of the thoracic and spinal deformities, and (2) relating these to total as well as regional ventilatory function, cough efficiency, and pulmonary vascular capacity. Serial observations over a period of time, as a kyphoscoliotic child grows into adulthood, would also be valuable Certainly studies of cardiopulmonary function in children with kyphoscoliosis should not be confused with similar studies in adults, in whom stabilization has occurred, and in whom repeated bronchopulmonary infections may have caused important permanent alterations in the lungs. If the kyphoscoliosis is due to poliomyelitis, the contribution of the residual muscular weakness to the impaired respiratory function is difficult to assess.

Until a better way of quantitating the thoracic deformity and evaluating the natural history in kyphoscoliosis is found, the consequences of kyphoscoliosis may be classified as follows.

1. The deformity is severe enough to cause such marked alveolar hypoventilation that the pulmonary hypertension and chronic cor pulmonale result mainly from the severe hypoxemia, hypercapnia, and polycythemia

2. The deformity is of an extent to cause not only alveolar hypoventilation but also anatomic restriction of the pulmonary vascular bed Pulmonary hypertension occurs with exercise as an expected result of an augmented blood flow through an anatomically restricted vascular bed

3. The deformity is severe enough to cause not only alveolar hypoventilation and often anatomic restriction of the pulmonary bed, but also impaired distribution of inspired air and mixed venous blood. Whether this distribution-perfusion disproportion is most marked in the overdistended lung or the compressed lung is not known at present.

4. While the deformity may cause alveolar hypoventilation, it is not severe enough to initiate the cardiopulmonary chain of events as described above. However, because of an impaired bronchial cleansing mechanism, bronchial and bronchiolar infection and obstruction are perpetuated, producing areas of obstructive pneumonitis with gradual deterioration of pulmonary integrity. Such changes would tend to further decrease alveolar ventilation.

Pectus excavatum, or *funnel chest*, is a thoracic deformity which only very rarely is associated with cardiac or pulmonary dysfunction. However, instances of severe pectus excavatum with heart failure, arrhythmias (especially atrial fibrillation), and catheterization findings demonstrating a pattern of right ventricular pressure similar to that in constrictive pericarditis, have been reported (Ravitch, 1951; Lyons et al., 1955; Wachtel et al, 1956) (see also Part 16, Chap. 12). In most instances, pectus excavatum becomes important because of the psychologic effect of its appearance and because of the abnormalities in the cardiac silhouette which often result in a mistaken diagnosis of heart disease. The heart is shifted to the left, the left middle salient is often prominent, and the transverse diameter of the heart may appear to be enlarged. A systolic murmur often may be heard over the precordium (Master and Stone, 1949; Edling, 1953).

Pectus carinatum, or *pigeon chest*, usually does not cause significant cardiac or pulmonary abnormalities The deformities of the chest produced by *thoracoplasty* do not lead by themselves to chronic cor pulmonale, unless there is extensive disease in the contralateral lung, usually diffuse obstructive emphysema

PICKWICKIAN SYNDROME. There has been an increasing recognition of a syndrome occurring in very obese individuals, which has been called *cardiopulmonary syndrome associated with obesity*, or the Pickwickian syndrome (a term applied by Burwell and associates, because of the startling resemblance of these patients to Mr. Wardle's boy, Joe, in Dickens' *Pickwick Papers*).

The clinical syndrome includes marked obesity, marked somnolence, twitching, shallow respirations, periodic breathing, secondary polycythemia, and chronic cor pulmonale (Sieker et al, 1955, Auchincloss et al, 1955, Burwell et al, 1956, Lillington et al, 1957). These patients suffer from anatomic restriction of the chest bellows as a result of their tremendous obesity. Their work of breathing is increased. The facts that their expiratory reserve volume tends to be low and that their lung approaches the expiratory position

further increase their work of breathing (Butler and Arnott, 1955). They develop a breathing pattern in which total ventilation, respiratory frequency, tidal volume, and alveolar ventilation are abnormally low The alveolar hypoventilation occurs as a result of the reduction in frequency in breathing, as well as the reduction in tidal volume, the latter causing a sacrifice of alveolar ventilation to dead-space ventilation They develop hypoxemia, hypercapnia, secondary polycythemia, pulmonary hypertension, right heart hypertrophy, and eventually failure. This syndrome appears in patients without intrinsic pulmonary disease Their respiratory centers are frequently unresponsive to the carbon dioxide stimulus, however, after weight loss, the center regains its responsivity. Some of the increased tolerance to carbon dioxide in these patients may be due to the fact that there is marked increase in the work of breathing, and it has been shown that an increased work of breathing greatly reduces the ventilatory response to inhaled carbon dioxide, even in normal persons (Chermack and Snidal, 1956). The entire syndrome appears to be reversible if the patient loses weight There is still some uncertainty as to all the factors involved in the pathogenesis of this syndrome Not all very obese patients demonstrate these abnormalities, it has been the author's observation that patients with this syndrome usually have short squat chests with short necks It is conceivable that these patients may also have some disorder of the central nervous system, possibly involving the hypothalamus and the respiratory center.

Insensitivity of the Respiratory Center. Patients have been described who demonstrate alveolar hypoventilation secondary to a diminished ventilatory drive from a damaged respiratory center They have normal hearts and lungs and normally functioning chest bellows They develop hypoxemia, hypercapnia, secondary polycythemia, right heart hypertrophy, and eventually failure They show an absence of dyspnea at rest and during exercise, in spite of the development of severe hypercapnia and hypoxemia. These patients show a low ventilatory response to exercise and inspired carbon dioxide Their cyanosis is aggravated by exercise but is abolished by hyperventilation or the breathing of high oxygen mixtures Pulmonary arteriovenous fistulas are therefore excluded The nature of the damage to the respiratory center is poorly understood but is considered to be inflammatory in some cases and vascular in others (Newman et al., 1951; Ratto et al , 1955, Pare and Lowenstein, 1956, Richter et al , 1957).

TYPE III: PULMONARY DISEASE WITH PREDOMINANT INVOLVEMENT OF THE VESSELS

This category includes those diseases in which the pathologic processes involve mainly the pulmonary vessels (intraluminal or extraluminal). (See the classification Causes of Chronic Cor Pulmonale, earlier in this chapter.)

Intraluminal Processes. In this category, the great restriction of the pulmonary vascular bed is the main cause of the high pulmonary vascular resistance, pulmonary hypertension, and the development of chronic cor pulmonale. There is usually very little ventilatory dysfunction present. However, the diffusion capacity of the lungs may be reduced by the loss of capillary surface area and by the reduced alveolar-capillary contact time, associated with the increased velocity of blood flow through the greatly narrowed pulmonary vascular bed (Luchsinger et al., 1957). *Cardiac output may be reduced, it cannot rise with exercise, and may even fall.*

This severe limitation of cardiac output is especially striking in *multiple recurrent small pulmonary emboli, thrombosis of the major pulmonary arteries,* and *primary pulmonary hypertension* It is responsible for some of the clinical manifestations seen in these patients. It explains the severe exertional dyspnea and weakness. Stimulation of sensory receptors in the pulmonary arteries by the marked increase in pulmonary artery pressure accompanying exercise may cause tachypnea, adding to the sensation of dyspnea (Aviado and Schmidt, 1955).

Exertional syncope occurs often. Various explanations for this symptom have been suggested (1) A *vasovagal reflex*, caused by impulses arising from the pulmonary arteries (Dressler, 1952, Dresdale, 1951, Aviado and Schmidt, 1955) (see Part 14, Chap 3). (2) A marked fall in coronary blood flow caused by an acute rise in right ventricular pressures (Schafer, 1956). (3) Acute failure of the right ventricle, due to a marked increase of pulmonary artery and right ventricular pressures with exercise The last explanation has been

supported by catheterization studies and is probably correct (Howarth and Lowe, 1953).

Episodic cyanosis frequently is present. Occasionally, such cyanosis is associated with a lowered arterial oxygen saturation, as a result of a right-to-left shunt through a valve-competent foramen ovale. However, peripheral cyanosis occurs often even when the arterial oxygen saturation is normal with a closed foramen ovale, because a high extraction of oxygen, consequent to the reduced cardiac output, leads to a high degree of oxygen unsaturation of the venocapillary blood (Shepard et al., 1957). It is, therefore, not due to arterial hypoxemia. Such peripheral cyanosis is noted whenever the blood flow is small in relation to the oxygen utilization of the tissues.

Precordial pain occurs and is usually associated with *dyspnea*. It is not relieved by nitroglycerin. This type of pain has been described in conditions associated with severe pulmonary hypertension and was named "hypercyanotic pulmonary angina" by Vaquez (1908). An identical type of chest pain occurs in any condition associated with severe pulmonary hypertension, such as mitral stenosis or congenital heart disease with severe pulmonary hypertension. Viar and Harrison believe that the pain is due to distention of the pulmonary artery (see also Chap. 7). Others feel that the pain is due to coronary insufficiency related not only to the severely restricted cardiac output but also to the increase in right ventricular pressures (Dresdale, 1951).

Multiple Recurrent Small Pulmonary Emboli. Multiple, repeated, small pulmonary emboli may be discharged over a long period of time, often without the usual clinical manifestations of pulmonary embolization. They are fed to the lungs from the peripheral veins (leg, pelvic, or prostatic veins) or occasionally from the right chambers of the heart. They may also arise from one or two large emboli which have lodged in a major pulmonary vessel. These multiple small emboli lead to a marked reduction in the extent of the pulmonary vascular bed, to pulmonary hypertension, and eventually chronic cor pulmonale (Castleman and Bland, 1946; Owen et al., 1953).

At necropsy, emboli in all stages of organization can be found, with changes reflecting the age of the emboli. Some vessels are filled with granulation tissue, some contain small recanalized channels, and, in some, the emboli have become organized in such a way as to resemble kidney glomeruli. With organization or recanalization, many of the vessels demonstrate changes which strongly resemble arteriosclerosis, particularly fibrous intimal thickening (Owen et al., 1953). Sometimes, only the most careful histologic studies will rule out primary arteriolosclerosis. Such cases were often considered in the past to be examples of primary pulmonary hypertension. These changes in the small pulmonary vessels have been reproduced experimentally in laboratory animals by the injection of various substances into the peripheral veins: macerated autogenous and heterogeneous blood clots, amniotic fluid, and bits of filter paper. The organization of these emboli leads to a type of fibrous intimal thickening often indistinguishable microscopically from localized arteriosclerosis (Wartman et al., 1951; Barnard, 1954; O'Neal and Thomas, 1955). In instances of multiple pulmonary emboli, arteriosclerosis, when found, is proximal to the occlusion, indicating that the hypertension was secondary to the occlusion. Atherosclerotic changes in the major pulmonary arteries may also develop. Because the right ventricle is often markedly dilated, many large mural thrombi may develop in the interstices of the trabeculae carneae, from which more emboli are often detached. Old organized emboli may leave as their only remainder thin fibrous bands bridging the lumens of the secondary and tertiary branches of the pulmonary artery (Castleman and Bland, 1946, Owen et al., 1953). Expansion of the circulation from the bronchial arteries occurs, as evidenced by marked thickening of the pleural and subpleural arteries which are derived from the bronchial arteries (Castleman and Bland, 1946). Often small healed pulmonary infarcts can be found also, which may be missed unless many subpleural sections of the lung are examined.

The clinical manifestations of repeated small pulmonary emboli are variable. While there may be evidence in the history of episodes which can be reconstructed as indicating pulmonary embolism, there may be absolutely no history of chest pain, hemoptysis, or recurrent pleural effusion. *Dyspnea* and *persistent cough* are usually prominent symptoms and may be present for as long as 7 years before the appearance of cor pulmonale and congestive failure (Owen et al., 1953). In Owen's study, patients with massive pulmonary artery thrombosis did not present any clinical features to distinguish them from those with emboli only

in the smaller vessels. Sometimes, the x-ray may be of help in that with massive pulmonary thrombosis, often a large bulky pulmonary artery shadow is seen with a rather sharp termination of a major branch. The peripheral arteries appear diminished, particularly in massive thrombosis of the major pulmonary arteries, in multiple, small pulmonary embolizations, the peripheral vascularity of the lung appears normal. In some instances, a foramen ovale, normally functionally closed, may become patent when right ventricular and atrial hypertension occurs. *Paradoxical embolism* then becomes possible. Such paradoxical embolism to the brain may produce focal signs, adding to the clinical picture produced by the disease process itself (Cabot, Case 44071).

The diagnosis of multiple pulmonary embolizations, as opposed to that of primary pulmonary hypertension, may be of some therapeutic significance. Kuida and associates feel that one should not make the clinical diagnosis of primary pulmonary hypertension during life, as it implies therapeutic nihilism. If multiple pulmonary emboli are suspected, every attempt should be made to stop their further appearance by prolonged anticoagulant therapy, or ligation of the appropriate veins.

Thrombosis of Major Pulmonary Arteries. Chronic cor pulmonale may result from massive thrombosis of the *major pulmonary arteries*. It was recognized quite early that such extensive autochthonous thrombosis of the main pulmonary artery or its major branches was associated with such fibrosing pulmonary diseases as extensive pulmonary tuberculosis or severe silicosis, atherosclerosis of pulmonary arteries, thromboangiitis obliterans involving the pulmonary artery (Hausner and Allen, 1940), cardiac failure with pulmonary hypertension, and conditions associated with hypercoagulability of the blood. *Most of the cases* now being recognized are secondary to massive pulmonary emboli (Hanelin and Eyler, 1951, Magidson and Jacobson, 1955, Ring and Bakke 1955). Moreover, the presence of one or more of the disorders which are associated with autochthonous pulmonary artery thrombosis does not always exclude the occurrence of pulmonary embolism, but [illegible]

[illegible] artery

In many instances, it has been difficult to understand the survival of these patients with so much obstruction in the pulmonary circulation. As indicated by Brenner (1935), as much as 75 per cent of the pulmonary cross-sectional diameter must be occluded before the systolic blood pressure falls, and 90 per cent, before death occurs. However, the appearance of the occluded pulmonary artery at necropsy may be misleading: during life, much blood may pass through the involved artery because of the distensibility of the vessel, unless the clot is adherent all around (Ring and Bakke, 1955). A very small lumen may be all that remains sustaining life, the final obliteration of this lumen causing death in many instances. Despite massive thrombosis, there is frequently notable absence of any massive infarction. This is probably related to the well-known expansion of anastomoses between the pulmonary and bronchial arteries, which has been demonstrated experimentally after ligation of the pulmonary arteries (Bloomer et al., 1949). However, infarcts are not uncommon and occasionally develop into *abscesses*. Thrombosis of the pulmonary artery has been reported in intraatrial septal defect, in patients who are in their sixth decade of life. It is conceivable that the presence of the intraatrial septal defect helped to prolong life in these cases, when the pulmonary arteries were occluded (Canada et al., 1953).

Clinically, the syndrome may be difficult to recognize. Often the underlying lesions of the lung or heart dominate the clinical picture. Early in the history, there is frequently, but not always, a picture resembling typical pulmonary embolism, with evidence for the source of the embolism being present. The clinical course may be acute, subacute, or chronic. Right heart hypertrophy and progressive, often intractable, right ventricular failure, are typical. Characteristic also is *dyspnea*, often completely out of proportion to the extent of the existing cardiac or pulmonary disease, and in the face of relatively clear lung fields. Severe *cough* and *retrosternal pain* may also be present. *Cyanosis* is not infrequent, and is often marked. *Syncopal attacks* or periods of *mental confusion* occur frequently. A *high-pitched systolic murmur* is frequently audible over the base (Magidson and Jacobson, 1955; Ring and Bakke, 1955).

The x-ray appearance of *massive* pulmonary artery thrombosis has been well described by Hanelin and Eyler: there is dilatation of the pulmonary artery proximal to the block, often with an abrupt *termination* or sharp *cutoff*,

corresponding to the tapering of the bulky portion of the thrombus. There are enlargement and alteration of the contour of the vessels at the level of the thrombus, which can best be described as unusual "lumpiness" There is a decrease in the size of the vessels distad to the thrombus, causing increased radiolucency of the corresponding area of lung. On fluoroscopy, hilar pulsation may be absent on the involved side. Very commonly involved is the right interlobar artery. Angiocardiography has demonstrated the obstruction well.

The incidence of this condition is probably greater than previously realized. While Magidson and Jacobson stated that massive thrombotic occlusion of the main pulmonary arteries was relatively rare, occurring perhaps once in 5,000 necropsies, in a series quoted by Hollister and Cull, 14 cases occurred in admissions to a 335-bed hospital over a 10-year period.

Sickle-cell Anemia. Repeated vascular thromboses in patients with sickle-cell anemia or sickle thalassemia may cause chronic cor pulmonale (Yater and Hansmann, 1936). In these patients, bouts of pleuritic chest pain or unexplained dyspnea, often considered to be caused by pneumonitis, are frequently *episodes of pulmonary infarction due to pulmonary arterial or arteriolar thrombosis.* Moser and Shea feel that cor pulmonale is most likely to develop in those individuals with (1) severe anemia or sudden lowering of the oxygen-carrying capacity and (2) a high percentage of S-hemoglobin. Favoring vascular thromboses also are such conditions as acidosis and left ventricular failure. Pulmonary arterial hypertension and right ventricular hypertrophy result from the high and fixed pulmonary vascular resistance. Since prolonged survival of even severely sicklemic individuals is becoming more common, more instances of this long-range complication of the sickle state will probably become apparent (Moser and Shea, 1957)

Schistosomiasis. Schistosomiasis is a rather frequent cause of chronic cor pulmonale in Egypt, South Africa, Asia, and Puerto Rico Massive and repeated embolization of the lung by the ova of the parasites, with an inflammatory response about the sequestrated ova, causes an extensive *obliterating endarteritis* (Shaw and Ghareeb, 1938). When the pulmonary infection is due to *Schistosoma mansoni*, hepatosplenomegaly with communications between the portal and systemic venous systems is invariably present; in infections with *Schistosoma hematobium*, the ova can pass directly to the lung. So-called angiomatoid structures have been described as typical for this disease (Shaw and Ghareeb, 1938; Girgis, 1952) Their exact function is as yet poorly understood.

Shaw and Ghareeb consider the angiomatoid structures to result from a growth in size of the blood spaces to cavernous dimensions beyond the confines of the original vessels, because of the loss of the controlling effect of the media of the arteries in which they develop. Others have considered them to be merely dilated anastomotic channels that develop between the pulmonary and bronchial vessels, and in some way an adaptation to the obstruction of the pulmonary circulation Some feel that the angiomatoid structures result from canalization of the occluding tissue by newly formed capillaries. Similar structures have been described in primary pulmonary hypertension (Kuida et al., 1957).

Angiocardiography has demonstrated a peculiar lacework aspect of the pulmonary vessels, as well as a persistence of the contrast medium in the lungs beyond the normal period of time after injection (de Faria et al, 1957). This prolonged retention of the dye in the lungs could well have been a feature of the severe increase in pulmonary vascular resistance, and has also been described in primary pulmonary hypertension.

Primary Pulmonary Hypertension. Chronic cor pulmonale may develop from hypertension in the pulmonary circuit in the absence of disease of the lung. In such cases the hypertension is considered to be primary, idiopathic, or essential (see Chap 7). These patients develop progressive right heart enlargement and right heart failure, and at necropsy show no signs of primary pulmonary disease, most of the advanced cases, however, show extensive changes in the pulmonary arterioles and arteries A considerable number of disseminated thromboses in the smallest pulmonary vessels are seen, but they are less extensive than the sclerotic vascular changes (especially intimal hyperplasia). It is believed that these sclerotic changes are *secondary* to some unknown factor causing an increase in pulmonary arterial pressure (Dresdale et al., 1951; Berthrong and Cochran, 1955; Kuida et al., 1957; Chapman

et al , 1957; Evans et al., 1957). While there has been a tremendous increase in the frequency of reports of this condition based on clinical and catheterization studies, it should be emphasized that a necropsy is an essential part of the final diagnostic procedure, since so many other conditions may simulate it. There have even been considerable variations of the pathologic picture at necropsy, so that it is quite likely that primary pulmonary hypertension *represents* not a homogeneous group but *a similar end-stage picture produced by diverse causes.*

Even after the most careful clinical study, the pulmonary hypertension at necropsy may be found to have been secondary to some structural malformation or disease which was previously unsuspected Recurrent silent pulmonary emboli are almost impossible to exclude from primary pulmonary hypertension by clinical means, and indeed often at necropsy.

Shepard et al. (1957) list the techniques that are necessary to exclude secondary pulmonary hypertension as follows (1) cardiac catheterization, (2) oximetry, (3) indicator dilution techniques, (4) inhalation of gas mixtures of different oxygen content, (5) radial and femoral arterial blood samples, (6) simultaneous recording of pulmonary and systemic arterial pressures, (7) pulmonary arterial wedge pressure To this might be added (8) left heart catheterization to exclude cases of "occult mitral stenosis" (Brachfeld et al., 1958)

Diffuse Pulmonary Vasculitis. Polyarteritis nodosa may cause chronic cor pulmonale if extensive diffuse vascular involvement of the lung is present Patchy pulmonary infarction due to vascular occlusion may complicate the picture Specific involvement of the coronary arteries may lead to myocardial infarction and may contribute to the final picture of cardiac failure In polyarteritis nodosa, the involvement is usually mainly of the medium-sized arteries, with the only extravascular lesions being infarcts secondary to occluded vessels However, there are other types of generalized vasculitis in which the involvement is mainly of smaller vessels (arteries, arterioles, veins, and venules), and in which extravascular lesions in other organs occur (parenchymatous changes in the spleen, focal glomerulonephritis) These conditions may also cause cor pulmonale when the pulmonary vascular involvement is extensive; the course is usually subacute.

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Other Causes of Intravascular Occlusions in the Lungs. Chronic cor pulmonale associated with pulmonary arteriosclerosis has been reported to have occurred in a patient with marked hyperglobulinemia, cryoglobulinemia, plasmocytosis, and glomerulitis. Proteinaceous masses occluding the small pulmonary arteries were found, which were considered to represent in vivo flocculation of cryoglobulin (Muirhead et al , 1952).

EXTRALUMINAL PROCESSES

This group includes conditions in which there is extensive granulomatous, fibrous, or neoplastic *infiltration of the interstitial tissue of the lungs.* Such infiltration greatly reduces the size and distensibility of the pulmonary vascular bed. This is the main cause for the development of pulmonary hypertension and chronic cor pulmonale. Characteristic of these conditions, when severe, is also a *reduction in the diffusion capacity of the lungs.* The diffusing capacity of the lungs is determined by the capillary surface area available for diffusion, the time interval allowed for equilibration along the alveolar-capillary membrane, and the character and thickness of the tissues constituting the alveolar-capillary barrier. Thickening of the alveolar-capillary membrane by [illegible]
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diffusing capacity. More recently, however, it has been pointed out that the reduction in diffusion capacity in many of these cases is the result not merely of the thickening of the alveolar-capillary membrane but also of the *increased velocity of blood flow through a greatly narrowed vascular bed with consequent critical reduction in the alveolar-capillary contact time.* In such cases, the contact time between alveolus and blood becomes insufficient to allow equilibration between alveolar and capillary oxygen tensions. The result is a widening of the alveoloarterial oxygen tension gradient, reflected in a desaturation of arterial blood, i e., a diffusion insufficiency (Rossier and Bühlmann, 1954; Luchsinger et al., 1957). The cases in this category also usually demonstrate moderate restrictive ventilatory dysfunction, lowered pulmonary compliance, reduced lung volumes, remarkably little reduction in maximum breathing capacity, and usually little or no abnormality in the distribution of inspired air However, Motley (1958) feels that some of the arterial blood oxygen desaturation on exercise in some of these patients is due to perfusion of blood through nonventilated or poorly ventilated areas These patients often show hyperventilation at rest and during exercise, resulting often in *low carbon dioxide tension* in the arterial blood Early, there is usually a normal arterial blood oxygen saturation at rest with marked reduction after exercise, eventually, resting *hypoxemia* develops, sometimes with *polycythemia*, which will increase the load on the right ventricle, just as it does in chronic diffuse obstructive emphysema (Austrian et al, 1951)

Early in the course of their disease, these patients may have a normal or only slightly elevated pulmonary arterial pressure at rest, developing a marked pulmonary hypertension on exercise This is probably mainly the consequence of the anatomically narrowed pulmonary vascular channels which accommodate an increase in pulmonary flow by a marked increase in pulmonary arterial pressure However, some contribution to the pulmonary hypertension must also be made by the exercise-induced hypoxia Eventually, pulmonary hypertension persists at rest. In the absence of cardiac failure, resting hypoxia, and polycythemia, *cardiac output in these patients is frequently found to be elevated.* It has been postulated that this high output in the absence of continual hypoxia is due to the increased metabolism resulting from the active interstitial inflammation in the lungs (Harvey et al., 1951), and the increased work of breathing, occasioned by the restrictive ventilatory defect While most of these patients die of pulmonary insufficiency, some eventually develop marked arterial oxygen desaturation and right heart failure, at which time *cardiac output is found to be low.* The pulmonary hypertension in these conditions usually cannot be reversed.

Sarcoidosis. The ways in which diffuse pulmonary involvement caused by extensive sarcoidosis may lead to chronic cor pulmonale have already been described In the second type, the granulomas are located predominantly interstitially, compressing arterioles and capillaries, as well as markedly thickening the alveolar-capillary membrane (see above). It should be stressed again that a complicating picture of diffuse obstructive emphysema may also be present, although a relatively "pure" form of alveolar-capillary block may be produced by this type of pulmonary sarcoidosis (Coates and Comroe, 1951; McClement et al, 1953, Stone et al, 1953; Marks et al., 1957).

Beryllium Disease. Beryllium disease with diffuse involvement of the lung may produce pathologic and functional derangements identical to those of sarcoidosis (Austrian et al, 1951, Marks et al., 1957). The term "beryllium disease" is preferable to the terms "pulmonary granulomatosis of beryllium workers" or "berylliosis" because the disease is truly a systemic intoxication, with biochemical abnormalities and involvement of the liver, spleen, kidney, and myocardium, as well as the lung.

The mechanism of disease production is comparable to that of a chemical intoxication, such as in lead poisoning, with changes attributed to hypersensitivity phenomena, rather than to a reaction, as in the pneumonoconioses The term berylliosis is completely misleading, because the disease is not produced by the inhalation of beryl ore. The disease-producing substances include beryllium metal, beryllium oxide, alloys of beryllium with other metals, and acid salts of beryllium While a history of exposure to beryllium, as in certain incriminated industrial operations, is extremely helpful, the diagnosis of beryllium disease can be proved only by discovery through spectrographic or chemical means of beryllium in

tissues which show granulomatous lesions (Hardy, 1956)

Histiocytosis X. Chronic cor pulmonale develops in histiocytosis X (eosinophilic granuloma), where the granulomatous infiltration is diffusely present in the lung. Here too, the granulomatous infiltration is located interstitially, causing marked thickening of the alveolar-capillary membrane, as well as restriction of the pulmonary vascular bed. Eventually, there also occurs obliteration of alveoli, with the formation of small nodules, often coalescing to form larger lesions.

All ages of lesions are simultaneously present. The granuloma is composed of monocytic histiocytes or macrophages, eosinophils, and multinucleated giant cells. There occur an increase in blood vessels, fibroblasts, and eventually necrosis and hemorrhage. Cholesterol appears in the histiocytes, causing a foamy appearance. The lesions may go on to resolution or fibrosis. The serum cholesterol level is normal. There is no blood eosinophilia, nor is there increase in serum globulin (Farinacci et al., 1951, May, 1954; Renzetti et al., 1957, Morton, 1957). End stages of the disease may present the picture of diffuse interstitial fibrosis, or honeycomb lung (polycystic lung). In the latter condition many emphysematous blebs develop, a result of either bronchiolar obstruction or scar retraction (Oswald and Parkinson, 1949). Spontaneous pneumothorax then frequently occurs as a complication.

Eosinophilic granuloma was first recognized in bone by Lichtenstein and Jaffe (1940). The possible relationship of this condition to Hand-Schuller-Christian disease and Letterer-Siwe disease was first pointed out by Farber. Eventually, the combination of skeletal and lung lesions was recognized. Lichtenstein (1953) proposed the term histiocytosis X to describe this category of disorders, the histiocytosis *referring to the essential type of histologic cellular reaction, and X referring* to the need for identification of an etiologic agent. Cases with only pulmonary involvement, and others with both skeletal and lung lesions have been described. The clinical differentiation between eosinophilic granuloma, Hand-Schuller-Christian disease, and Letterer-Siwe disease depends, therefore, on differences in the location, number, and extent of individual lesions and on the differing rates of progression of the disease. They should no longer be listed with the primary disorders of lipid metabolism, along with Niemann-Pick and Gaucher's disease. The etiology is unknown. It is quite possible that this group of diseases presents a common histologic picture produced by varying causes. A similar situation obtains in tuberculosis, sarcoidosis, and beryllium disease, where similar pathologic conditions result from widely differing etiologies.

Eosinophilic granuloma of the lung occurs usually in a young adult. Dyspnea and cough appear early, and eventually the patient appears chronically ill. While positive scalene lymph node and bronchoscopic biopsies have not been reported yet, positive histologic specimens may eventually be obtained by these methods. Therapy is as yet unsatisfactory. There have been reports of temporary remission with the use of antibiotics; later reports have shown antibiotics to be disappointing. Steroids have occasionally been observed to help. X-ray therapy has been useful for localized bone lesion.

Hematogenous Tuberculosis. During the acute phase of hematogenous pulmonary tuberculosis, the inflammatory involvement of the alveolar-capillary septa may produce alveolar-capillary block. In very advanced cases, sometimes a marked increase in the venous admixture is found. With effective antituberculous therapy, these abnormalities of oxygen transfer are reversed, correlating well with the resolution of the acute exudative process. In severe cases, after clinical recovery, a pattern of mild restrictive ventilatory insufficiency may persist, and pulmonary hypertension may occur with mild exercise (Mc Clement et al., 1951). This indicates that, in some instances, the scarring of healed miliary tuberculosis may be sufficient to result in the obliteration of a very large proportion of the pulmonary vascular bed. It is probable that eventually cases will be studied which will have gone on to the development of chronic cor pulmonale.

Wegener's Granulomatosis. Chronic cor pulmonale has been described in Wegener's granulomatosis. This is a disease of unknown etiology with pathologic changes suggestive of a hypersensitivity reaction. It is characterized by three features: (1) necrotizing granulomatous lesions in the upper and lower respiratory tracts, (2) generalized focal necrotizing vasculitis involving both arteries and veins, almost always present in the lungs, and often widely disseminated in other sites; (3) glomerulitis with necrosis, thrombosis, capsular adhesions, and granulomatous changes (Wegener, 1936, Fahey et al., 1954). The disease

diffusing capacity. More recently, however, it has been pointed out that the reduction in diffusion capacity in many of these cases is the result not merely of the thickening of the alveolar-capillary membrane but also of the *increased velocity of blood flow through a greatly narrowed vascular bed with consequent critical reduction in the alveolar-capillary contact time.* In such cases, the contact time between alveolus and blood becomes insufficient to allow equilibration between alveolar and capillary oxygen tensions. The result is a widening of the alveoloarterial oxygen tension gradient, reflected in a desaturation of arterial blood, i.e., a diffusion insufficiency (Rossier and Buhlmann, 1954, Luchsinger et al., 1957). The cases in this category also usually demonstrate moderate restrictive ventilatory dysfunction, lowered pulmonary compliance, reduced lung volumes, remarkably little reduction in maximum breathing capacity, and usually little or no abnormality in the distribution of inspired air However, Motley (1958) feels that some of the arterial blood oxygen desaturation on exercise in some of these patients is due to perfusion of blood through nonventilated or poorly ventilated areas These patients often show hyperventilation at rest and during exercise, resulting often in *low carbon dioxide tension* in the arterial blood Early, there is usually a normal arterial blood oxygen saturation at rest with marked reduction after exercise, eventually, resting *hypoxemia* develops, sometimes with *polycythemia,* which will increase the load on the right ventricle, just as it does in chronic diffuse obstructive emphysema (Austrian et al, 1951)

Early in the course of their disease, these patients may have a normal or only slightly elevated pulmonary arterial pressure at rest, developing a marked pulmonary hypertension on exercise. This is probably mainly the consequence of the anatomically narrowed pulmonary vascular channels which accommodate an increase in pulmonary flow by a marked increase in pulmonary arterial pressure However, some contribution to the pulmonary hypertension must also be made by the exercise-induced hypoxia. Eventually, pulmonary hypertension persists at rest. In the absence of cardiac failure, resting hypoxia, and polycythemia, *cardiac output in these patients is frequently found to be elevated.* It has been postulated that this high output in the absence of continual hypoxia is due to the increased metabolism resulting from the active interstitial inflammation in the lungs (Harvey et al, 1951), and the increased work of breathing, occasioned by the restrictive ventilatory defect. While most of these patients die of pulmonary insufficiency, some eventually develop marked arterial oxygen desaturation and right heart failure, at which time *cardiac output is found to be low.* The pulmonary hypertension in these conditions usually cannot be reversed

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ent (see below). While basal subcrepitant rales are audible, there is a striking paucity of physical signs in view of the x-ray findings. Roentgenologically, there is usually an increase in the density of the hilar and vascular markings, with eventually bilateral diffuse reticular mottling and superimposed fine nodulation. With intercurrent infections, infiltrations due to bronchopneumonitis appear. *Clubbing* is frequent. *Polycythemia* may be present, especially late. The major physiologic disturbances are those that occur with the alveolar-capillary block syndrome and moderate restrictive ventilatory dysfunction. Death is usually due to pulmonary insufficiency, right heart failure, or terminal bronchopneumonitis. Treatment should always include the use of the adrenal corticosteroids or their analogues, because of their known retarding effect on fibroblastic proliferation. However, until tried, it is impossible to predict their effectiveness in any single patient. Sudden death has been described following the abrupt termination of steroid therapy (Rubin and Lubliner, 1957).

Idiopathic Pulmonary Hemosiderosis. Idiopathic pulmonary hemosiderosis (Ceelen's pulmonary hemosiderosis) may cause chronic cor pulmonale. The etiology is unknown.

The lung shows an increase in reticulum, collagen, and smooth muscle, fragmentation of the elastic tissue in the alveolar walls and small blood vessels, and recent and old hemorrhages, with many hemosiderin-filled macrophages. There is a marked increase in the amount of iron in the lung. Severe interstitial fibrosis and thickening of the alveolar walls eventually develop. Cases have been mistaken for the Hamman-Rich syndrome.

Idiopathic pulmonary hemosiderosis usually occurs in children and young adults. Acute episodes are characterized by severe cough with massive hemoptysis and dyspnea. Remissions and exacerbations are characteristic. There then develop increasing exertional dyspnea, easy fatigability, severe anemia and reticulocytosis, and sometimes jaundice. Siderocytes may be seen in the sputum and in a lung biopsy. Chronic cor pulmonale with right heart failure frequently develops. Death is usually from respiratory failure.

Radiation Fibrosis of the Lungs. Chronic cor pulmonale has been reported in radiation fibrosis of the lungs (radiation pneumonitis). Usually, it is a large amount of radiation given in a brief period of time to both lungs that leads to this condition. The damage begins with injury to the alveolar walls and capillary endothelium, with edema, followed by proliferation of alveolar and capillary endothelium and fibroblastic proliferation in the alveolar walls. This is followed by obliteration of the alveoli, with marked thickening of the alveolar capillary septa, peribronchial and perivascular fibrosis, and disruption of pulmonary elastic tissue. The pathologic picture is aggravated by the development of bronchial obstruction due to bronchial reaction with areas of atelectasis and pneumonitis (Warren and Spencer, 1940, Brown, 1956). The pattern of pulmonary dysfunction is that of the alveolar-capillary block syndrome with a markedly reduced or restricted pulmonary vascular bed (Stone et al., 1956). When the damage is severe, such patients show progressively severe dyspnea and productive cough, fever, right heart failure, and pulmonary insufficiency.

Diffuse Pulmonary Interstitial Fibrosis Caused by Obstruction of the Pulmonary Veins. There have been reports of an unusual form of interstitial pulmonary fibrosis due to chronic obstruction of the pulmonary veins. The most common cause of the pulmonary venous obstruction has been a dense collagenous or keloid-like mass in the mediastinum, apparently a result of a healed posterior mediastinitis. Chronic pulmonary venous obstruction with similar pulmonary changes, due to a large myxoma of the left atrium, a large left atrial thrombus, or congenital stenosis of the pulmonary veins, has also been reported. The extensive pulmonary changes are usually seen only in the portions of the lung in which pulmonary veins have been constricted by the collagenous mass in the mediastinum. When the process is extensive enough, chronic cor pulmonale develops (Edwards and Burchell, 1951, Andrews, 1957; Bindelglass and Trubowitz, 1958). In its most fully developed form, the interstitial pulmonary fibrosis is found to be identical to that occurring in the late stage of the Hamman-Rich syndrome.

Andrews suggests that in any case of unexplained pulmonary interstitial fibrosis, the pulmonary veins and their atrial orifices be very care-

appears usually in patients in the fourth and fifth decades of life, without histories of allergy, asthma, or exposure to sulfonamides. The onset is frequently with a severe or often destructive sinusitis or rhinitis, followed by what appears to be a persistent pneumonitis. Signs of renal damage and generalized vasculitis accompany or follow these respiratory symptoms. Pulmonary hypertension and chronic cor pulmonale develop frequently. Specific involvement of the myocardium and the presence of pulmonary infarction due to vascular occlusion may complicate the picture (Fahey et al., 1954). The disease is usually fatal, running a course of from 6 months to 2 years.

Pneumonoconiosis. In severe *asbestosis, extensive interstitial fibrosis* is the main cause of the pulmonary hypertension and the resultant chronic cor pulmonale.

In *silicosis,* chronic cor pulmonale develops much more frequently when there is the complicating presence of *diffuse obstructive emphysema,* and here the changes are like those in chronic cor pulmonale due to chronic obstructive emphysema alone, except that the cardiac output tends to be normal or low (Thomas, 1951, Harvey et al., 1951, Wells, 1954b). However, chronic cor pulmonale has occasionally been recorded in silicosis without significant chronic obstructive emphysema, where the silicotic nodules appear to be located mainly about vascular channels, often also with extensive conglomerate scarring. Here, usually, arterial oxygen desaturation is *not* present at rest, appearing only on exercise; cardiac output tends to be normal or low (Harvey et al, 1951). *Thrombosis of the major branches of the pulmonary artery* frequently occurs in severe silicosis and contributes to the reduction in the pulmonary vascular bed (Wells, 1954)

Collagen Diseases (see Part 16, Chap 3). Chronic cor pulmonale has been observed in scleroderma when the involvement of the lung has been diffuse and severe (Taubenhaus et al, 1955). It is associated with the syndrome of alveolar-capillary block (Austrian et al., 1951). Cases of dermatomyositis have been reported in which degenerative and occlusive changes in the small pulmonary arteries and arterioles caused severe pulmonary hypertension and right ventricular hypertrophy (Cald well and Aitchison, 1956). Disseminated lupu erythematosus has been noted occasionally t be associated with sufficient pulmonary vas cular involvement to cause chronic cor pu monale (Wood, 1952).

Diffuse Interstitial Pulmonary Fibrosis. Di fuse interstitial pulmonary fibrosis (Hammar Rich syndrome) usually causes chronic c pulmonale. The etiology is unknown Wh clinically and pathologically the end stages this syndrome represent an entity, it is mo probable that it is in fact a heterogeneo group, with many etiologies.

Early, there is a *non-granulomatous interstit pneumonitis* associated with marked hyperpla and metaplasia of the alveolar cells, sufficien striking sometimes to resemble adenomatosis. T inflammatory changes in the alveolar walls co tinue to the eventual deposition of fibrous tiss with further thickening of the alveolar walls, that they may encroach on the alveolar spac Usually, very little inflammatory exudate is se in the alveoli, except in the presence of a comp cating bronchopneumonitis. Eventually, diff induration of both lungs with a fine meshwork relatively acellular fibrous tissue occurs Howev even in far-advanced cases, foci may be se showing the exudative and cellular features scribed above and indicating continued activity of the disease process (Hamman and Rich, 1944, Schechter, 1953, Rubin and Lubliner, 1957) The focal scarring, emphysematous bleb formation, and bronchiolar necrosis often evolve into the picture of shrunken fibrotic lungs with multiple small air cysts, bronchiolectasis, and bronchiectasis (honeycomb lung) (Oswald and Parkinson, 1949, Rubin and Lubliner, 1957).

This condition is more common in males; it occurs most frequently between the ages of 30 and 50 but has been reported at all ages The duration of symptoms varies from 6 months to over 6 years. It is apparent that by the time severe symptoms appear, the disease has been present for many months and often years Clinically, there is progressive dyspnea and cyanosis, thoracic pain, frequent hemoptysis, and a nonproductive cough. Weight loss and fever occur, especially when there is superimposed pneumonitis Eventually expectoration appears, becoming profuse and occasionally bloody. The usual physical signs associated with pulmonary hypertension are pres-

nized as acute cor pulmonale (Mack et al., 1950).

COMBINATIONS OF TYPE I THROUGH TYPE III

In many instances, structural and functional abnormalities of more than one category may coexist in a patient, contributing to the development of chronic cor pulmonale. For example, in *sarcoidosis*, even when the involvement tends to be localized primarily about the pulmonary vessels, there may be sufficient peribronchial granulomatous infiltration to have produced a significant degree of diffuse obstructive emphysema. However, examples in which the involvement is almost exclusively of one or the other type have been reported. In *silicosis*, too, while predominant vascular involvement is very important, the complicating diffuse obstructive emphysema is often the major reason for the development of chronic cor pulmonale. In some cases of severe *kyphoscoliosis*, functional abnormalities pertinent to all three categories exist. For example, a case of severe kyphoscoliosis may show some anatomic reduction of the pulmonary vascular bed, particularly in areas where there is compression of the lung, alveolar hypoventilation due to marked restriction of the chest bellows, and diffuse airway obstruction with chronic obstructive emphysema.

DIAGNOSIS

It is almost impossible to make an early diagnosis of chronic cor pulmonale because of the difficulties in recognition of early right heart enlargement. While pulmonary hypertension must exist for some time before right ventricular hypertrophy develops, its clinical recognition in a patient with chronic pulmonary disease justifies the presumptive diagnosis of chronic cor pulmonale.

Clinical Examination. Clinical evidence of chronic cor pulmonale appears late in the course of the disease. In chronic diffuse obstructive emphysema, the overdistended lungs make it difficult to detect the usual signs of pulmonary hypertension and right ventricular enlargement. The heart tones are often faint. The existence of chronic cor pulmonale should, therefore, be suspected in patients with chronic obstructive emphysema of more than minimal degree. By the time arterial blood gas abnormalities become demonstrable, chronic cor pulmonale may be assumed to be present. The presence of *secondary polycythemia* is thus usually good evidence that right ventricular hypertrophy has already developed (Harvey et al., 1951).

Clubbing of the digits and pulmonary hypertrophic osteoarthropathy do not necessarily indicate the presence of chronic cor pulmonale since they may occur with small local lesions in the lung, such as bronchogenic carcinoma or fibrous mesothelioma. They are more frequently present when severe suppurative bronchiectasis coexists with the diffuse obstructive emphysema.

The mechanisms involved in the production of clubbing of the digits are as yet poorly understood. However, it has been demonstrated that an *increased blood flow* exists through the clubbed digits which is in excess of physiologic requirements and is largely passing through the numerous arteriovenous anastomoses in the distal segments. The direct passage of blood from digital arteries into the deep venous plexus of the digits is held to account for the structural changes observed in clubbed digits. Clubbing is a reversible condition, and in those conditions where a reduction of the circulation to the fingers is possible, regression of the clubbing occurs. This has been reported after the removal of pulmonary tumors (Mendlowitz, 1942, Wilson, 1952).

Arrhythmias, with the exception of nodal tachycardia, are unusual in chronic cor pulmonale. *Pleural effusions* due to congestive failure are rare; if they occur, a postpneumonic empyema or pulmonary infarction should be suspected. *Moderate elevation of peripheral venous pressure* in the absence of congestive heart failure may occur because of the increased intrapleural pressure present in many patients with chronic obstructive emphysema; however, marked elevation of venous pressure is usually a sign of right heart failure. By the time the usual peripheral signs of right ventricular failure appear, the recognition of right heart involvement becomes easy.

When overdistended lungs or thoracic deformity do not interfere with the examination, and when the pulmonary artery pressure is quite high, striking findings often appear. This is especially true in such conditions as multiple recurrent small pulmonary emboli and primary pulmonary hypertension. Examina-

fully examined. He also pointed out the similarity of the changes of this condition with those that occur in idiopathic pulmonary hemosiderosis. There are dense interstitial fibrosis with marked thickening of the alveolar capillary membrane, and marked narrowing of many of the arterioles and smaller arteries by medial hypertrophy and intimal proliferation. Some of the vascular narrowing is clearly the result of thrombosis However, such thrombotic changes are secondary, since it is known that pulmonary arterial and arteriolar thromboses do not produce interstitial fibrosis of this type. Where there is sparing of the pulmonary veins of one or more lobes, these lobes show normal arteries, arterioles, and the absence of the interstitial fibrosis

Edwards and Burchell postulated that the occlusive arterial and arteriolar lesions in the lobes with severe venous obstruction act to protect the pulmonary capillaries from excessive passive congestion This condition cannot be reproduced experimentally by acute obstruction of the pulmonary veins, since apparently chronic long-standing obstruction is necessary. The clinical picture is not sufficiently typical to make the diagnosis readily. Varying murmurs may be heard over the heart. Most striking is the development of progressive dyspnea, cough, and repeated massive hemoptyses. There may be *recurrent pulmonary edema*, and eventually intractable right heart failure develops (Andrews, 1957, Bindelglass and Trubowitz, 1958)

Polycystic Disease of the Lungs. Diffuse polycystic disease of the lung, sometimes described as *honeycomb lung*, is often the end stage of many conditions in which there is diffuse interstitial infiltration of the lung with eventual development of interstitial fibrosis (Oswald and Parkinson, 1949). It has thus been observed in sarcoidosis, histiocytosis X, diffuse granulomas of unknown etiology, and the Hamman-Rich syndrome Cases of diffuse involvement of the lung with miliary cysts satisfying the criteria for congenital hereditary origin have been described by McKusick and Fisher. Similar congenital cystic disease of the lung has been observed in Marfan's syndrome and tuberous sclerosis. These patients develop recurrent pneumonitis and often spontaneous pneumothorax Carcinomatous degeneration has been reported. McKusick and Fisher stress the fact that the pulmonary lesions may be completely silent, escaping clinical detection for many years. However, clubbing of the digits or more advanced types of hypertrophic pulmonary osteoarthropathy may be present in these patients for many years before subjective or objective pulmonary signs appear

Metastatic Carcinomatosis of the Lung. Metastatic carcinomatosis of the lung may lead to chronic cor pulmonale in several ways Extensive perivascular lymphatic spread (endolymphatic carcinomatosis or lymphangitic carcinomatosis) often causes a carcinomatous endarteritis as well as external mechanical compression of the arteries and arterioles by the desmoplastic character of the cords of carcinoma cells (Storstein, 1951). Extension into the interalveolar septa may also produce varying degrees of alveolar-capillary block. Multiple emboli, composed of either tumor tissue or blood clots from the deep leg veins, may further reduce the pulmonary vascular bed. Local vascular thromboses in the lung also often occur to reduce further the vascular bed. Occasionally, distention of the pulmonary lymphatic vessels may give rise to the presence in the x-ray of horizontal linear densities in the periphery of the lung bases (Levin, 1959). In extensive carcinomatosis, the presence of severe anemia may prevent the appearance of central cyanosis. When the progression of events leading to right heart enlargement and failure is very rapid, the term *subacute cor pulmonale* has been applied (Greenspan, 1934, Brill and Robertson, 1937; Mason, 1940)

Other Diffuse Interstitial Infiltrations of the Lung. Also reported to cause chronic cor pulmonale are the following conditions: far-advanced farmer's lung, pulmonary interstitial granulomatosis of unknown etiology, and diffuse bronchiolar carcinoma of both lungs (adenomatosis)

Extrinsic Compression of the Main Pulmonary Arteries. Compression of the main pulmonary artery trunk or its stems has been recorded to cause chronic cor pulmonale. This has been described with an aneurysm of the concave portion of the ascending aorta and with tuberculous calcified or neoplastic hilar lymph nodes Should rupture of the aneurysm of the aorta into the pulmonary artery occur, this sudden development of a left-to-right shunt will lead to all the abnormalities recog-

Electrocardiography. Like all other techniques, the electrocardiogram gives evidence for the diagnosis of chronic cor pulmonale late; it does, however, give such evidence earlier than the roentgenogram. In addition to the usual leads, special precordial leads over the right chest (V_4R, V_5R) give valuable additional information The changes most frequently seen in chronic cor pulmonale due to chronic obstructive emphysema are those which are not themselves pathognomonic of right ventricular hypertrophy. As a result of the overdistended lung and the depressed diaphragms in chronic obstructive emphysema, *the heart assumes a more vertical position, and is rotated clockwise about its longitudinal axis, sometimes with backward displacement of its apex*

This is usually manifested in a mainly inverted *QRS* complex in aVL and an upright QRS complex in aVF, and a shift of the transitional zone over the precordium to the left, with the presence of S waves in all the limb leads and the persistence of S waves *in* leads V_5 and V_6 Sometimes the QRS complex will be of *the QS type in* V_2 *and* V_3, because of the marked clockwise rotation *of* the heart, and may simulate the residual *changes of* an old transmural anteroseptal infarct The QRS complexes may sometimes exhibit *low voltage,* especially in the precordial leads. This may be because of the increased volume of air-containing lung between the heart and chest wall, or because of a positional change in the heart, so that the direction of the QRS vector becomes *perpendicular* to the frontal plane All these changes often simulate or are exaggerated by the presence of right ventricular hypertrophy or dilatation, since right ventricular enlargement will produce the same kind of rotation of the heart as the pulmonary changes associated with chronic emphysema (Zuckerman et al, 1948).

When, in a patient with *chronic obstructive* emphysema, *P pulmonale* is present with these changes, the diagnosis of *chronic cor pulmonale* becomes extremely likely, even though these changes per se are *not the result* of hypertrophy of the right ventricle

P pulmonale (Shleser and Langendorf, 1942, Katz and Pick, 1956) is a tall, peaked P wave in leads II, III, and aVF (Fig 13-28) Usually it is also seen to be small in lead I, inverted in aVL, and often diphasic (plus-minus) *in* V_1 *and* V_2 It is often associated with a depression of *the* P-Q segment owing to the prominent negative T_p waves This is apparently a secondary T-wave change, since it is associated with a high-voltage upright P wave. The exact mechanism for its production is unknown While in some cases, it may be associated with hypertrophy or dilatation of the right atrium, it frequently is present when *these are absent. In* some patients, P pulmonale will *revert to* normal after intensive treatment. In most cases, it is probably *due to a positional* change, in a markedly vertical heart with a low diaphragm, the apex is displaced *in such a way* that higher upright P-wave potentials, ordinarily facing towards the back or other parts, are now directed to the feet.

It has been reported in normal persons that complexes with secondary R waves (*r'*) *are found* in V_4R in about 50 per cent of cases. If more *right-sided* leads are taken (V_5R, V_3R, *and an* interspace above and below as well), more than 50 per cent show an r'. These are especially frequent when the leads are *placed* one interspace below However, in normal persons, usually the S wave is larger than either R deflection, and usually the r' is smaller than the R (*Camerini* and Davies, 1955). Probably the r' represents activation of the conus of the right ventricle, since it has been known for some time that the conus of the right ventricle and the posterobasal portion of the left ventricle are the last parts of the myocardium to be activated (Lewis and Rothschild, 1915, Barker et al, 1930).

The appearance of an M-shaped QRS complex (rsR'), with R' *taller* than r, in leads over the right precordium (V_4R, V_1, and V_2), which has been called *incomplete right bundle branch block* by *some* investigators, is usually good evidence *of right* ventricular "strain" and hence of chronic cor pulmonale (Fig 13-27). *In* some cases, complete right bundle branch block, with QRS duration longer than 0.12 sec, may also result *from* right ventricular involvement *in* chronic *cor* pulmonale.

The presence of a *typical* right ventricular hypertrophy pattern (a relatively tall, late R *in* V_4R or V_1) *is* usually definite evidence of chronic cor pulmonale (Myers et al, 1948) (Fig 13-28). *An R wave in* aVR is not sufficient The tall R *may sometimes* be preceded by a tiny Q wave.

The relationship between the type of *overload on the right ventricle* and the type of electrocardiographic evidence of heart *strain* has been described by Cabrera and Monroy,

tion of the heart may reveal displacement of the apex beat to the left, but with an enlargement of the right ventricular type, i.e., a systolic heave over the right ventricular outflow tract. *The 2d sound at the pulmonic area is loud and split,* and often easily palpable. Various murmurs are frequently heard and are often difficult to differentiate from those present in congenital or acquired heart disease. A *systolic murmur* over the base is common. Frequently present is *the Graham-Steell murmur* of pulmonary insufficiency. A *mid-diastolic murmur* may be heard in the 4th left interspace or over the apex; it probably corresponds to a "right-sided Austin-Flint murmur." Wood (1952) has stressed that the peripheral pulse is usually small and the systemic blood pressure low, with the systolic and diastolic pressures approaching the mean He also has stressed the appearance of *giant A waves* in the jugular venous pulse. Left vocal cord paralysis, due to compression of the left recurrent laryngeal nerve by a dilated main or left pulmonary artery, has been noted.

Roentgenologic Examination. Roentgenologic signs of chronic cor pulmonale, while also rather late in appearing, are suggestive earlier than the clinical findings In addition to the usual roentgenographic studies (posteroanterior, both oblique, and lateral projections), careful fluoroscopic examination is of special value because it may aid in the simultaneous assessment of pulmonary function The earliest abnormality to become apparent is *enlargement of the pulmonary artery trunk and its main stems* This abnormal dilatation is due to the pulmonary arterial hypertension, and must be differentiated from the normal prominence of the pulmonary artery trunk in a vertically placed heart, which is rotated clockwise about its longitudinal axis This positional change of the heart is the usual one occurring in chronic obstructive emphysema, in which the diaphragm is depressed and the lungs are overdistended The enlargement of the pulmonary artery trunk is best seen with the patient in the right anterior oblique position. When the dilatation becomes more marked, it becomes visible as a convexity of the left middle salient in the posteroanterior projection Hilar dance is usually not present, since the degree of augmentation of pulmonary blood flow necessary to produce this phenomenon is usually not found in chronic cor pulmonale. Calcification of pulmonary arterial atheromas may rarely be seen. *Right ventricular enlargement* usually is first seen in the right anterior oblique and lateral projections as an anterior bulging in the region of the outflow tract or pulmonary conus of the right ventricle, encroaching on the retrosternal space. It should be noted that by the time the enlargement of the right ventricle is demonstrable in x-rays, dilatation is already present, *hypertrophy of the free wall of the right ventricle alone cannot be detected roentgenologically in chronic cor pulmonale.* If concomitant marked left ventricular enlargement is present, the detection of associated right ventricular enlargement may be difficult, because retrosternal encroachment by the enlarged left ventricle may simulate that due to an enlarged right ventricle. An increase in the transverse diameter of the heart in the posteroanterior projection usually appears very late or not at all, and is due to displacement of the left ventricle; the right ventricle is still anteriorly located and never forms part of the left border of the cardiac silhouette in this view. The development of congestive failure will often make apparent a dilated superior vena cava and an enlarged right atrium. Except for its occasional use to exclude congenital heart disease or to localize an arteriovenous fistula in the lung, angiocardiography has not been particularly useful in the diagnosis of chronic cor pulmonale

Cardiac Catheterization (see Chap. 4). Right heart catheterization is the best method for the early detection of pulmonary hypertension. While it cannot be recommended as a routine diagnostic procedure, its use in combination with pulmonary function tests and blood gas studies may be very helpful in management It may be necessary to rule out the presence of congenital heart disease or mitral stenosis While the presence of pulmonary hypertension is not *prima facie* evidence of the presence of right ventricular hypertrophy, for practical purposes, its presence, especially at rest, in a patient with considerable chronic pulmonary disease justifies the assumption that right ventricular hypertrophy has already developed.

wise rotation of the heart about its longitudinal axis) or *ischemia of the anterior wall of the heart* That the first mechanism is probably operating most often is borne out by the observation that after successful treatment in some cases, not only do these T waves become upright, but a shift in the transitional zone over the precordium to the right, and a reduction in size of the S waves in the limb leads and in V_5 and V_6 also occur. This is not associated with demonstrable change in position of the diaphragm, but congestive failure has been eliminated, and hence presumably right ventricular dilatation has been reduced. Absence of a prolonged Q-T interval may help rule out anteroseptal infarction when the T waves are inverted over the right precordium, since it has been reported that the Q-T interval is normal in patients with chronic cor pulmonale in the absence of other types of heart disease (Alexander et al., 1951).

TREATMENT

The treatment of chronic cor pulmonale today has much to offer. The unselective pessimistic attitude of the past arose from a failure to differentiate among the various causes of chronic cor pulmonale, the imperfect understanding of the pathologic physiology of the condition, and the failure to separate symptoms due to the pulmonary disease from those due to cardiac failure. Moreover, newer techniques in the treatment of bronchopulmonary disease are now available. When the chronic cor pulmonale is due to diffuse obstructive emphysema, in which many of the pathologic and physiologic changes are partially reversible, real improvement will frequently result from

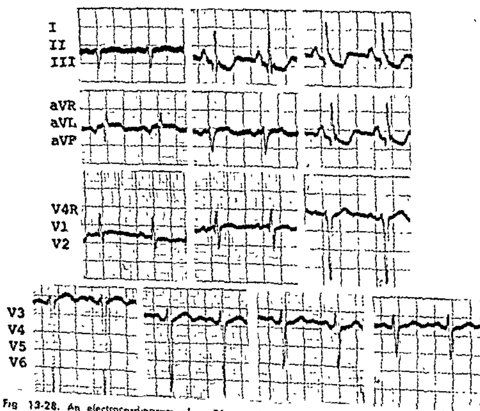


Fig 13-28. An electrocardiogram of a 56-year-old male patient with bronchiectasis, severe chronic diffuse obstructive emphysema, and chronic cor pulmonale (necropsy) Sinus rhythm P pulmonale The QRS complex is mainly inverted in leads I and aVL, and upright in leads II, III, and aVF, an R wave is present in aVR The S-T segment is depressed in leads II, III, and aVF, and slightly elevated in aVR and aVL Electric position is vertical A tall late R' wave is present in leads V_4R and V_1, preceded by a tiny r and s. A deep S wave persists out to V_6 There is a marked shift of the transitional zone over the precordium to the left. This is a right ventricular hypertrophy pattern

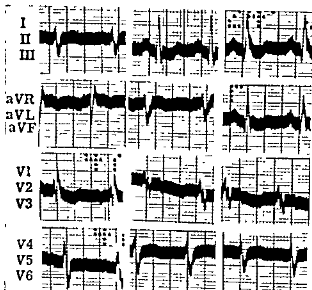


Fig. 13-27. An electrocardiogram of a 53-year-old male patient (I C.) with bronchiectasis, chronic diffuse obstructive emphysema, secondary polycythemia, and chronic cor pulmonale Sinus rhythm The QRS complex is mainly inverted with a broad S wave in leads I and aVL, and upright in leads II, III, and aVF. A late R wave is present in aVR The S-T segment is depressed in leads II, III, and aVF, and slightly elevated in aVR and aVL Electric position is vertical An M-shaped QRS complex is present in leads V_1 and V_2 (rsR'). A deep broad S wave is present in leads V_4 through V_6. There is a marked shift of the transitional zone over the precordium to the left. This is so-called incomplete right bundle branch system block, and is good evidence for right ventricular hypertrophy

and Donzelot et al. For example, in interatrial septal defect, a "diastolic overload" pattern is usually seen (rsR'), while in congenital pulmonic stenosis a "systolic overload" pattern is usually found (tall R wave over right and much of left precordium, with depressed S-T segment and inverted T wave). The first type of right ventricular enlargement pattern ("diastolic overload," i e , rsR' over the right precordium) occurs somewhat more frequently in chronic cor pulmonale due to chronic obstructive emphysema (Fig 13-27), while the second type ("systolic overload," i.e , tall, late R wave over the right precordium) occurs more often in chronic cor pulmonale due to pulmonary disease with predominant involvement of the vessels (Mack and Snider, 1956) This may be a manifestation of the greater frequency of *augmented input loading* of the right ventricle in the first type of chronic cor pulmonale, in which hypervolemia and increased cardiac output are more common However, this simple relationship is complicated by the fact that in chronic cor pulmonale due to chronic obstructive emphysema, resistance overloading also occurs because of the increase in pulmonary vascular resistance and pressure. Moreover, with the development of right ventricular failure and dilatation of the right ventricle, diastolic overload occurs even in chronic cor pulmonale due to pulmonary disease, in which the pathologic condition is largely localized in or about the pulmonary vessels.

Suggestive electrocardiographic changes and those definite for right heart hypertrophy occur in chronic cor pulmonale only when the hypertrophy is marked. When electrocardiographic evidence of right ventricular hypertrophy is present, the latter is almost always found at necropsy (Myers et al., 1948; Johnson et al., 1950), but in the majority of cases, particularly when the hypertrophy is slight or moderate, no definite right ventricular hypertrophy pattern is seen in the electrocardiogram. Not all the reasons for the electrocardiographic changes in right ventricular hypertrophy are yet understood. While positional changes are important in influencing the contour, they are certainly not the sole cause. The mechanism by which an acute increase in work of the right ventricle, usually associated with dilatation of the chamber, produces the so-called "strain pattern" is also not understood

The spatial vectorcardiogram in some cases may show a typical pattern of right ventricular hypertrophy when the electrocardiogram is equivocal or negative. It may also help differentiate right ventricular hypertrophy from right bundle branch block (Elek et al, 1954, Stern and Tenney, 1956). However, the changes in heart position produced by diffuse obstructive emphysema often obscure the pattern of right ventricular hypertrophy in the spatial vectorcardiogram (Stern and Tenney, 1956). Frequently the presence of a right ventricular strain pattern is associated with the presence of inverted T waves in leads V_2 through V_4. These often become upright after treatment. The reason for the inversion of these T waves is not fully understood as yet They may be caused by *right ventricular dilatation* (reflecting merely an increased clock-

trations, intermittently, well-humidified, and only if the patient is under constant observation by a physician Control of the oxygen therapy will depend on its observed effect on the frequency and depth of respiration, the clinical appearance of the patient, and finally, wherever possible, on serial determinations of the arterial blood gases. The latter techniques are important, since the clinical appearance of the patient may be deceptive If arterial blood gases cannot be measured, the carbon dioxide content and pH of the venous blood will be of some aid It is often necessary to use some *mechanical aid to respiration* in order to hyperventilate the patient, in an attempt to "wash out" retained carbon dioxide at the same time that oxygen is being administered The various types of *intermittent positive-pressure respirators* are useful in this regard.[2] Some of them require the patient's own spontaneous inspiratory effort to start the inspiratory cycle, and, if the patient's respiratory rate is adequate, they may be used with oxygen. However, if the patient tends to develop respiratory depression or apnea, a compressed air tank may be substituted for the oxygen tank, or an apparatus used which cycles automatically. When the situation is more critical, it may be necessary to use a *tank respirator*, a measure which requires meticulous nursing care and constant attention (Boutourline-Young and Whittenberger, 1951; Barach et al, 1952, Harvey et al, 1953, Segal and Attinger, 1955) Mechanical respiratory aid may have to be continued, usually intermittently, for several weeks, since the carbon dioxide stores in the body are not confined to the blood alone but include those present in all the body fluids as well, especially the fat (Nichols, 1957).

Respiratory depressant drugs, such as *morphine*, are strongly contraindicated When the patient's condition becomes less critical, attempts should be made to improve his ventilatory function by training him in the more effective use of his diaphragm (*breathing exercises*, Miller, 1953), pneumoperitoneum and abdominal belts have been disappointing in their results.

Mechanical cough devices, devised by Barach and Beck (1954), using exsufflation with negative pressure, have been useful to produce hyperventilation and to raise secretions from the tracheobronchial tree. A *tracheostomy* may be required to permit removal of secretions which the patient cannot raise, it will also diminish the dead space. It may be used with an intermittent positive-pressure breathing apparatus. In some cases, the tracheostomy becomes permanent. Overholt and Segal have employed elective long-term tracheostomy in some patients with extensive bilateral bronchiectasis. For patients requiring permanent tracheostomy and repeated catheter aspiration of the deeper airways because of ineffective cough and profuse secretions, an operation developed by Rockey and associates (1956) holds promise. It involves the creation of a skin-lined cervical tracheocutaneous communication guarded with airtight external skin valves (tracheal fenestration). It permits phonation and cough but can be opened at will for aspiration.

The carbonic anhydrase inhibitor, *acetazoleamide*, has sometimes proved useful in the treatment of patients with chronic cor pulmonale and hypercapnia, with or without congestive failure (Nadell, 1953, Bell et al., 1955, Galdston and Geller, 1957). This drug decreases the alkali reserve (plasma bicarbonate) by promoting the excretion of bicarbonate and bicarbonate-bound base by the kidney. Because it produces a metabolic acidosis, it should *not* be used in the presence of severe acidosis Acetazoleamide also decreases the partial pressure of carbon dioxide in the arterial blood. This is probably because of improved alveolar ventilation, since the drug has been reported to increase the response of the respiratory center to the carbon dioxide stimulus, especially if intravenous aminophylline is also given (Taquini et al, 1957; Galdston and Geller, 1957). Acetazoleamide also acts as a mild diuretic, being more efficient in the congestive failure of chronic cor pulmonale than in that associated with other types of heart disease (Schwartz et al, 1955). It has also

hypoventilation

While there has been good evidence that *salicylates* in large doses stimulate respiration (Tenney and Miller, 1955; Wegria et al.,

[2] It should be kept in mind that, if used continuously, these respirators will tend to decrease cardiac output.

treatment. Where the chronic cor pulmonale is due to pulmonary disease with the pathologic condition localized mainly in or about the pulmonary vessels, the outlook for treatment is less favorable.

Treatment of Chronic Cor Pulmonale Due to Chronic Diffuse Obstructive Emphysema. Intensive treatment of the bronchopulmonary disease is as important as, and usually more important than, specific cardiac measures. Congestive heart failure can be alleviated only by at least partial reversal of many of the pathologic changes in the lung which are responsible for the anatomic reduction in the pulmonary vascular bed and the hypoxia. This is accomplished by combating infection, producing an adequate airway, and improving effective alveolar ventilation These goals are interdependent, so that the measures employed have multiple effects

Antibiotics should be given promptly in an attempt to control infection, which frequently was the precipitating cause of the breakdown. The sputum should be cultured, and sensitivities of the significant organisms to various antibiotics determined However, one should not wait for the results of such studies before administering antibiotics. Necessary changes of the antibiotic may be made after the results of the sensitivity studies are known

Tetracycline appears in the sputum in high concentration and is especially useful, if *penicillin* is given by injection, it should also be administered by *aerosol*, since it is not excreted in the sputum sufficiently. Resistant micrococci have been unusually troublesome and, if present, will require treatment with such drugs as *chloramphenicol, erythromycin*, or *novobiocin*.

Bronchodilator drugs are invaluable for aiding bronchial drainage, helping control infection, and improving ventilation The sympathomimetic amines, isoproterenol (*Isuprel*), racemic epinephrine (*Vaponephrin*), and phenylephrine (*Neo-synephrine*), are best given by *aerosol*, usually mixed with normal saline solution or a detergent solution, at least four times daily. Where effective inhalation does not occur, intermittent positive-pressure breathing devices may be useful to help deliver the aerosol. Theophylline ethylenediamine (*aminophylline*) is very useful, especially when given, well diluted, by slow intravenous drip; it is also effective when given rectally, especially as a retention enema. *Ephedrine* orally is also an effective bronchodilator. It may be necessary to use corticotropin, adrenal corticosteroids, or their analogues, but their potential disadvantages should be recognized

Sputum liquefaction is aided by overcoming dehydration, humidification of room air, and frequent inhalations of mist produced by the nebulization of water or detergent solutions. If the sputum is unusually purulent and viscid, aerosols containing *proteolytic enzymes* (*pancreatic dornase*) may be helpful. *Potassium iodide* is an excellent expectorant Cough and expectoration should be facilitated. Antitussive medication should be used minimally or not at all. Where basal bronchiectasis is present, *postural drainage* may be of great help, although the patient is often too sick to permit it *Endotracheal aspiration* with a soft rubber catheter may be lifesaving; in some cases, bronchoscopy and even tracheostomy will be necessary.

The respiratory center in these patients is usually unresponsive to either increased partial pressure of carbon dioxide or increased hydrogen ion concentration in the arterial blood, apparently because of a selective depression of the respiratory center to these stimuli. If the hypercapnia has been of long duration, this poor ventilatory response to the carbon dioxide stimulus is usually not reversible, even though the partial pressure of carbon dioxide and the alkali reserve in the arterial blood are restored to normal levels (Tenney, 1954; Cohn et al, 1954; Fishman et al , 1955). Yet the respiratory center still responds to afferent stimuli from special receptors in the muscles, since exercise still causes increased ventilation. It is also still responsive to afferent stimuli from the carotid and aortic bodies, so that the tachypnea, which is necessary in these patients, is often maintained mainly by some degree of hypoxemia. *The use of pure oxygen consistently depresses ventilation*, thus having a different effect than when given in concentrations sufficient merely to correct the hypoxemia towards the physiologic range (Fishman et al., 1955). *The use of 100 per cent oxygen may thus lead to hypoventilation, with carbon dioxide retention, acidosis and death*. Nevertheless, because of the disastrous consequences of severe hypoxemia, the administration of oxygen is frequently mandatory. It should then be given *in lower conce*

ties, they frequently herald impending pulmonary and circulatory breakdown These may be prevented by intense therapy. While the acute respiratory infection which often initiates a downhill course in these patients is usually originally of viral origin, it is the bacterial superinfection which lingers and is eventually the most disturbing For this reason, in those patients in whom repeated respiratory infections occur, the use of small doses of broad-spectrum antibiotics, daily or several times weekly, especially during the winter, may be very valuable (McVay and Sprunt, 1953). It is often advisable to interrupt such prophylactic treatment periods to permit the reestablishment of normal saprophytic flora

Treatment of Chronic Cor Pulmonale Due to Chronic Alveolar Hypoventilation Syndromes. In this group of conditions, treatment of right heart failure includes the usual cardiac measures and phlebotomy However, no success will be achieved unless alveolar ventilation is improved *Respiratory depressant drugs, such as morphine, and even the barbiturates, should be avoided* Relief of the hypercapnia may restore the sensitivity of the respiratory center to the carbon dioxide stimulus Relief of the hypoxemia takes much of the burden off the heart Oxygen may be used but with care not to depress respiration and increase carbon dioxide retention Mechanical respiratory aids, such as the intermittent positive-pressure breathing devices, are therefore often necessary An intercurrent acute bronchitis may be a major catastrophe for these patients, often abruptly causing severe hypoxemia, hypercapnia, and right heart failure At this time, not only should antibiotics and bronchodilators be used, but a tank respirator may be necessary

Treatment of Chronic Cor Pulmonale Due to Predominant Involvement of the Pulmonary Vessels. Therapy of chronic cor pulmonale in patients with pulmonary disease in whom the disease tends to be localized in or about the pulmonary vessels is unsatisfactory. When bronchopulmonary infection or chronic obstructive emphysema is present as a complication, it should be treated intensively. The latter especially may complicate such conditions as silicosis and diffuse pulmonary sarcoidosis. Harvey and associates (1953) have advised continuous marked restriction of physical activity in these patients as one of the few procedures which can be employed to reduce the strain on the right heart, since the pulmonary vascular bed is restricted in a permanent anatomic manner. In multiple recurrent small pulmonary emboli, thrombosis of the major pulmonary arteries, and probably *primary pulmonary hypertension*, *continuous anticoagulant therapy* should be used. *Priscoline* and the *ganglionic blocking agents* have been disappointing In these conditions, also, the pulmonary vascular bed is so restricted that great caution must be used in the administration of intravenous fluids, the injection of small *amounts of fluid* has been reported to cause *cyanosis*, collapse, and death (Cross and Kobayashi, 1947). When the essential functional abnormality is alveolar-capillary block without hypercapnia, *oxygen* in high concentrations *may* be given When there is interstitial infiltration with granulomas which will respond to specific medication, such as the *adrenal corticosteroids*, such medication should be employed. However, it is usually impossible to predict whether resolution or fibrosis of these granulomas will occur

1955), their clinical usefulness in the treatment of the hypercapnia of patients with pulmonary insufficiency has not been demonstrated. Furthermore, in patients with chronic diffuse obstructive emphysema, the stimulation of respiration may be disadvantageous if the work of breathing is increased beyond a critical level, so that the augmented work of the respiratory muscles increases carbon dioxide production beyond the capacity of the lungs to eliminate it (Otis, 1954; Riley, 1954; Bader and Bader, 1955) Far more rational is therapy directed at reducing the work of breathing by methods listed above or by the use of a mechanical respirator.

Patients with chronic cor pulmonale in congestive failure and respiratory acidosis are critically ill. They are often difficult to manage As a result of hypoxia and hypercapnia, they are frequently somnolent, confused, and combative Cerebrospinal fluid pressure is often increased, even to the extent of producing papilledema (Mithoefer, 1952, Patterson et al., 1952) Restoration of alertness is of prime importance, since it will permit more effective coughing and expectoration of sputum and greater cooperation with therapeutic procedures.

Cardiac therapy will be effective only if combined with the above pulmonary measures *Digitalis*, contrary to earlier reports, has been shown to definitely improve cardiac performance in patients with chronic cor pulmonale and congestive failure (Ferrer et al, 1950), and is therefore indicated *Mercurial diuretics* and *salt restriction* should also be employed, with attempts to avoid electrolyte imbalance Initially, *bed rest* is extremely important to reduce the body's metabolic requirements; the arterial blood oxygen saturation in these patients falls markedly with exercise. Yet immobilization favors shallow breathing and retention of bronchial secretions *Phlebotomy* becomes important in the presence of polycythemia The possible advantages and disadvantages of polycythemia and of the associated hypervolemia have been discussed above. Since the red blood cells in secondary polycythemia are often hypochromic, consideration should be given to the hemoglobin as well as to the red blood cell counts and hematocrit. Bleeding is advisable when the hematocrit is above 55; 300 to 500 cm^3 of blood may be removed every 3 to 5 days to bring the hematocrit down to 50, and the hemoglobin to about 14 Gm Since many of these patients have associated arteriosclerotic or hypertensive heart disease, the presence of some degree of left ventricular failure, due to these associated conditions, will often result in a particularly gratifying response to specific cardiac therapy.

Surgical excision of localized giant bullae has been performed in patients with severe emphysema and cor pulmonale Clinical benefit was seen in those patients who had already developed resting hypoxia and right heart failure (Fitzpatrick et al., 1957). *Thyroid ablation* by large doses of radioactive iodine has been used to lower the basal oxygen requirements of the body tissues in some very severe cases of diffuse obstructive emphysema. Significant improvement in some patients has been reported (Bercu and Mandell, 1954, Hurst et al., 1955).

Peptic ulcer has been noted to occur with much greater frequency in patients with chronic obstructive emphysema than in the general population (Fulton et al., 1952, Weber and Gregg, 1955; Mack and Snider, 1956). Barium studies of the upper gastrointestinal tract should therefore be performed routinely, they are particularly important if corticotropin or adrenal corticosteroid therapy is to be employed, since these drugs notoriously cause reactivation of peptic ulcer

Prophylactic therapy in patients with chronic diffuse obstructive emphysema is of the utmost importance They should be examined at regular intervals and advised to report immediately any of the following danger signals acute respiratory tract infection, fever or malaise, purulent sputum, hemoptysis, and chest pain They should know the purpose of each of their medicaments Chronic bronchitis must be attacked vigorously, not only by a studied medical regime but also by corrective manipulation of the environment. This includes attention to industrial safeguards, air pollution, poverty, and health education. *Smoking should be forbidden.* In patients with diffuse obstructive emphysema, acute respiratory infections should be treated as major illnesses. Not only may their effects be cumulative and lasting, but with signs of increasing pulmonary dysfunction, polycythemia, and blood gas abnormali-

ties, they frequently herald impending pulmonary and circulatory breakdown. These may be prevented by intense therapy. While the acute respiratory infection which often initiates a downhill course in these patients is usually originally of viral origin, it is the bacterial superinfection which lingers and is eventually the most disturbing. For this reason, in those patients in whom repeated respiratory infections occur, the use of small doses of broad-spectrum antibiotics, daily or several times weekly, especially during the winter, may be very valuable (McVay and Sprunt, 1953). It is often advisable to interrupt such prophylactic treatment periods to permit the reestablishment of normal saprophytic flora.

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The blood in cor pulmonale

MARIO STEFANINI AND STEPHEN C. MATHEWSON

The subject of this chapter finds its practical importance in the increasing occurrence of cor pulmonale. An autopsy survey in an area in the United States has shown 6 3 per cent cases of cor pulmonale due to pulmonary emphysema in 790 cases with heart disease (Scott and Garvin). In an industrial area in England, among 300 patients, cor pulmonale was found responsible for congestive heart failure in 8 5 per cent of the females and 40.5 per cent of the males (Flint). These figures justify the statement by many cardiologists that *cor pulmonale represents today the fourth most common disease of the circulatory system*, following rheumatic, coronary, and hypertensive heart disease.

For the purpose of this discussion, cor pulmonale is defined as the right ventricular hypertrophy which develops as result *of increased* resistance to the flow of blood through the pulmonary circulation, because of pathologic conditions in the lungs or in the pulmonary vessels. This definition excludes enlargement of the right ventricle due to any other cause, such as left ventricular failure and congenital or acquired diseases of the myocardium, endocardium, or pericardium Cor pulmonale (see classification, Causes of Chronic Cor Pulmonale, in Chap 8) may be *acute* (as it occurs in massive pulmonary embolism), *subacute* (as it may be occasionally seen in metastatic carcinoma or lymphoma of the lung with fine parenchymal dissemination), or *chronic* Chronic cor pulmonale may be produced by two essential mechanisms: (1) *chronic obstructive emphysema;* (2) *chronic disease of the pulmonary arterial vessels.* This discussion will be limited to chronic cor pulmonale, as this has the most profound effects on the bone marrow and on the blood.

The mechanism of production of chronic cor pulmonale also deserves some discussion, as it has important bearing on the intensity and frequency of blood complications. Whatever the cause, the cross-sectional diameter of the pulmonary bed is reduced at first, and the capacity of the small pulmonary vessels to distend is consequently diminished. In the emphysematous type, external compression of the capillaries by bullae, and shrinkage and distortion of the vascular bed because of pericapillary exudation, necrosis, and scarring, are the most important mechanisms In the predominantly vascular type, endoarterial diseases, such as embolization and arteritis, *primary* pulmonary hypertension, or involvement of the interstitial tissue, are all important. The loss of cross-sectional area leads to increased resistance to the flow of blood through the pulmonary vessels and to *hypoxia* (quite rapidly in the emphysematous type, much later in the vascular type of cor pulmonale). Also, the increased resistance to blood flow through the lung causes prompt elevation of the right heart output As the volume of venous return to the heart increases, there is an additional burden on the right ventricle A vicious circle is established, with ever-increasing hypoxia.

THE BLOOD AND BONE MARROW

The present section will be limited to a general discussion of the fundamental aspects

of the hematologic abnormalities in cor pulmonale *It may be stated that, in general, significant hematologic changes in cor pulmonale occur only after decompensation and heart failure have set in.* The central mechanism, as in congestive heart failure, is *hypoxia* The reasons why hypoxia leads to changes in blood, plasma proteins, serum electrolytes, etc., are similar to those which apply in congestive heart failure and in congenital cyanotic heart disease Yet, blood changes seen in cor pulmonale are usually more pronounced than those seen in congestive heart failure, *because of the combined features of primary hypoxia and heart failure.*

Red cell count, hematocrit, hemoglobin, and reticulocytes are remarkably increased. In fact, hematocrit values of 60 per cent or more are not uncommon. As the hematocrit rises, the blood viscosity also increases and the blood sedimentation rate drops (especially if there is concomitant fibrinogenopenia) On the other hand, white cell and platelet counts are usually normal[1] The bone marrow reflects the increased erythropoietic activity with marked hyperplasia of the erythroid elements Isotopic studies indicate an accelerated iron turnover and considerable increase in red cell mass With high red cell mass, blood volume is usually high Plasma volume is, at least *in the beginning, normal* Later, however, as decompensation sets in, *hypervolemia* may develop because of increased volume of circulating plasma and of interstitial and, possibly, *intracellular* fluid owing to kidney involvement and retention of sodium, a situation which will be discussed in the chapter on congestive heart failure (see Part 18) *In general,* plasma volumes are higher *in* patients with cor pulmonale following *correction* of congestive failure and polycythemia (Lewis et al , 1954), and both blood and plasma volumes fall after successful digitalization (Ferrer et al , 1950)

[1] Occasionally, leucocytosis, neutrophilia, and thrombocytosis may be found in patients who have become cyanotic and acidotic because of cor pulmonale The underlying primary disease may cause elevation of serum carbon [illegible]

[illegible]

PLASMA PROTEINS

Changes seen in the protein composition of plasma are, in general, similar to those which accompany congestive heart failure.

BLOOD GASES AND ELECTROLYTES

Analysis of blood gases and serum electrolytes in patients with cor pulmonale reveals the changes due to pulmonary dysfunction and *circulatory* impairment. Arterial oxygen saturation and oxygen tension are lower than normal. The oxygen saturation is generally of 70 per cent or less, a situation known to lead to *polycythemia.* There is higher than normal arteriovenous oxygen gradient in these patients while at rest, which increases during exercise. Also, with severe pulmonary disease, *the carbon* dioxide retention may be marked, and respiratory acidosis may be seen. Under these circumstances, *the serum* chloride level *is reduced.*

Renal plasma flow and glomerular filtration rate are decreased, as they *generally* are in congestive heart failure, but only if *congestive* heart failure or polycythemia is present. Retention of sodium then occurs, with all the consequences already described *in Part 18.*

HEMORRHAGIC AND THROMBOTIC COMPLICATIONS

In general, the incidence of hemorrhagic and thrombotic complications in cor pulmonale *seems* lower than in congestive heart failure. The authors have seldom *seen* a case of cor *pulmonale* complicated by truly severe hemorrhagic manifestations, even following emergency surgery. The incidence of *thrombosis* is, on the other hand, higher. Although no statistical figures are available, phlebothrombosis of the deep leg veins is *not uncommon* in cor pulmonale, at least *in* the authors' experience Many of the pathogenetic factors are those of *congestive* heart failure, including *the* fact that most patients with cor pulmonale are in the age group in which phlebothrombosis is most frequent. Also, the disease is debilitating and forces the patients to a great deal *of rest,* which deprives them of the stimulus *to* venous return represented by the muscular contraction Additional factors are particular to cor pulmonale Hunter et al. have rightly emphasized the importance *of normal* negative

intrathoracic and abdominal pressures to prevent phlebothrombosis. In emphysema, intrapleural negative pressure is decreased, and this, in turn, delays the venous return to the right side of the heart. Also, prolonged expirations and poor thoracic excursions do not encourage proper venous return. Methods of therapy, such as pneumoperitoneum and abdominal binders, enhance the stasis in the lower extremities. In addition, hypoxemia produces venous endothelial damage, which, in turn, encourages clot formation (McLachlin and Paterson). Finally, when severe decompensation exists, other factors, such as the prolongation of the circulation time and the occurrence of venous stasis, may lead to phlebothrombosis.

As will be described in congestive heart failure, *intravascular clotting probably occurs continuously in these patients during life.* In fact, occasional evidence of silent premortal intravascular clotting is found at autopsy in patients with cor pulmonale. Expression of continuous intravascular clotting may also be the moderate thrombocytopenia and fibrinogenopenia, the decreased activity of labile factor, and the mild activation of the fibrinolytic system which are occasionally found in these patients.

Clinical experience seems to indicate that patients with cor pulmonale are especially prone to thrombotic accidents in the wake of surgery. The prevention of this complication is best achieved by venesection, to reduce as much as possible the hematocrit value without aggravating the hypoxia.

1

Acute and chronic hypotension

LOUIS F. BISHOP AND JEROME NOBLE

Hypotension connotes a level of blood pressure below that which is considered normal. It becomes obvious, immediately, that this normal level must be defined before a blood pressure reading may be regarded as "low" Furthermore, it is generally agreed that a variation in blood pressure below any statistically accepted norm is not necessarily associated with complaints on the part of the patient The mere objective finding of "low" blood pressure by the examining physician in the absence of subjective complaints or other positive physical findings may be regarded as of no clinical significance Occasionally, the physician may unwittingly cause unjustifiable concern in his patient by relating this finding during the course of an office consultation (*iatrogenic hypotension*).

For the purpose of clarity and understanding, an attempt was made to classify the various hypotensive categories in the following outline (Scott, R W, et al)

I. Essential hypotension (not associated with any demonstrable disease state)
   A. Asymptomatic
   B. Constitutional
II Secondary hypotension
   A. Acute secondary hypotensive states
      1. Shock
         a Metabolic
         b Surgical
         c Traumatic
         d Cardiogenic
         e Miscellaneous, medical
      2. Carotid sinus syndrome
      3. Acute infectious diseases
      4 Hypotensive drugs and anesthetics
      5. Hysteria
      6. Cough syncope
      7. Effort syncope due to primary pulmonary hypertension
      8 Hypoxia
      9 Strenuous exercise
      10. Chronic valvular disease of the heart
      11. Hypotension in aviation
      12 Heat exhaustion and heat stroke
   B. Chronic hypotension
      1. Primary idiopathic orthostatic hypotension
      2 Secondary—chronic orthostatic hypotension as a result of
         a Sympathectomy (postsympathectomy syndrome)
         b Central nervous system disorders
         c Chronic debilitating diseases
      3 Endocrinopathies
      4. Chronic cardiac disorders

ESSENTIAL HYPOTENSION

Asymptomatic. This group includes persons who present themselves to the physician for a routine checkup or are examined by physicians for insurability. In these cases, the patient or applicant for insurance is completely symptom-free, and hypotension is merely an incidental finding.

Statistically, the incidence of hypotension is practically unknown Insurance companies know that "the *mortality* rate among persons with blood pressures below the average is significantly lower than that among persons with so-called 'normal blood-pressure.'" As for *morbidity*, one insurance company will refuse a policy if the applicant's pressure is "more than 40 mm below average." However, for the most part, it is thought that "low blood pressure, in the absence of accompanying disorders, is not regarded as of much import."

Another insurance company feels that "hypotension never kills, only fills the mind with anxiety; usually not charged an extra premium. If diastolic pressure is below 60, there is a strong possibility of aortic regurgitation" (personal communications).

The earlier literature did not consider hypotension to be of significance (Bishop, 1904; Faught, 1913, Norris et al., 1927). A resurgence of interest in the subject is indicated in more recent European literature (Gallavardin, 1945; Lassance, 1954) and in the current abstracting and indexing compilation of the periodicals

As mentioned above, a symptom-free individual, whose physical findings are completely within normal limits except for hypotension, cannot be regarded as hypotensive until a normal range of blood pressure is established As may be anticipated, there are many factors to be considered in establishing this norm Blood pressure values vary from race to race, Eastern Asiatics, for example, show lower readings in all age groups than do Europeans or Americans. Pressures vary in accordance with sex Women between puberty and menopause on an average have lower pressures than men of corresponding age After the menopause, however, females have higher average blood pressures than males in similar age groups In a large sampling of apparently healthy men and women of ages ranging from 65 to 106 years (Master et al.), the "mean blood pressure was 145/82 for men and 156/84 for women." After the age of 74, the systolic pressure declines slowly in women and remains constant in men The mean diastolic pressure shows little variation from the ages of 65 to 80 and tends to decline thereafter

According to one representative insurance group, the following are the *minimal* normal pressures in accordance with ages.

Ages	*Systolic*	*Diastolic*
10–19	90	50
20–39	100	55
40–up	110	60

Finally, in summing up the viewpoint of another insurance group appraising hypotension, "hypotension is not a disease but an anomaly. Its deviation below average may or may not be abnormal Moderate hypotension, say down to 100 mm systolic, is compatible with good health; down to 90 mm, in many instances even down to 80 mm, abnormality may not be assumed . . . not a few persons with 90/60 readings are in excellent health" (personal communications).

Constitutional Type. This category of hypotensive persons includes those who have symptoms that may be related to their blood pressures. Some have *poor work capacity, poor resistance* to physical strain, and extreme sensitivity to weather changes They may be inefficient, easily fatigued industrial workers, poor soldiers, etc. They are not debilitated or malnourished and have no laboratory or clinical stigmata of organic disease states. They may, however, complain of *headaches, dizziness,* and easy *fatigability* They may show poor muscular development and may be of sedentary habit. As a constitutional type, they are frequently of the asthenic habitus Although their prognosis as to longevity is excellent, they may be *poor surgical risks,* and also may be more prone to severe *occlusive complications* with the onset of advancing arteriosclerotic blood vessel changes.

Evidence has been presented indicating the existence of an association between body builds and blood pressures by comparative statistical investigative studies (Weiss, A.). One thousand hypertensive persons, 1,000 normotensive persons, and 1,000 hypotensive persons were selected at random from 100,000 men ranging in age from 56 to 60 They were subjected to body-measurement studies (somatometry). The results were compared and statistically analyzed No correlation was found between height and blood pressure However, an unequivocal correlation existed between the circumference of the thorax and the blood pressure Respiratory excursions were greatest in the normotensive and smallest in the hypertensive groups The height-width index (body height/average thoracic circumference) was greater in hypotensive persons and showed decreases in hypertensive persons, while the reciprocally proportional thoracic circumference increased in going from the hypotensive to the hypertensive groups. Body weight showed an evident increase with increasing blood pressure The height-weight index (body height in centimeters over 100 cm/body weight in kilograms) decreased with an increase in blood pressure

As summarized, the data indicated that *the thin, small-chested individual (asthenic) is statistically most commonly the constitutionally hypotensive individual*

Hypotension and its implications have received more attention in the foreign literature than in that of the United States. A syndrome in which hypotension not associated with other symptoms or signs other than lassitude, decreased fitness, empty feeling in the head, and a tendency toward dizziness and bouts of sweating occurring in the morning has been reported (Svartz). It is considered an isolated sign, which responds to treatment and tends to improve as the day progresses, the blood pressure generally increasing towards evening.

"Acquired permanent hypotension" and its effect upon work efficiency is a subject of considerable investigation in other countries. The effect of hypotension upon industrial workers has been the subject of recent studies carried out in Italy (Piazza et al; Bonsangue). Initially, Ferrannini (1903) commented upon primary hypotensive states Subsequently Bishop (1904), Hertz, Muenzer, Goodman, Martinet, and others considered the syndrome of permanent idiopathic arterial hypotension. Pal, Bard, Gallavardin, Herz, Alvarez, Borach, Yoachim, Munk, and later Friedlander, Luisada (1929), Kisch, and still others studied the etiology and pathogenesis of this condition Pellegrini (1952) studied this syndrome further after perusing the literature and decided that it was secondary to a deficiency in arterial and arteriolar tone The problem, however, remained unsolved and was generally referred to as "idiopathic," in so far as mechanism and physiology were concerned

Following World War II, this syndrome has become increasingly prevalent The condition was studied in working classes It was found that certain electrical workers developed weakness and dizziness upon climbing ladders

These workers were found to have an average diastolic blood pressure of 100 mm. The phenomenon was studied more intensively in 400 workers, aged 18 to 40 They were found to be normal psychiatrically and organically Of this group, 192 were considered hypotensive. It should be noted that these investigators considered 115 mm Hg to be the lower limits of normal The following blood pressures were found 37 per cent, 115 mm, 31.70 per cent, 110 mm, 13 54 per cent, 105 mm, 11 95 per cent, 100 mm; 3 12 per cent, 95 mm, and 1.56 per cent had blood pressures of 90 mm. These persons had been observed for many years prior to the time of this study, and documentary proof in each case indicated that their blood pressures had been above 115 mm *in the past.*

It was considered that the present hypotension was an acquired state secondary to unknown factors which had resulted from innate individual mechanisms. It was finally concluded that this phenomenon represented poor cardiovascular tone. An additional 200 subjects were selected at random in a subsequent study, and it was found that 114 of these, likewise, had blood pressures of 115 mm or less. They had been observed for 3 to 11 years, and there was clinical documentation regarding their physical status and their subjective complaints. It was concluded that persons suffering from "acquired idiopathic permanent hypotension" may be potentially poor work risks in hazardous occupations; *e.g.*, if they are electrical workers they tend to suffer dizziness while climbing ladders.

Physiologic Mechanisms in Essential Hypotension. The physiologic mechanisms which result in the physical finding of hypotension reflect the summation of homeostatic processes constantly in operation, such as cardiac output, the tonus of the peripheral vascular bed, and the oxygen requirement of the body as a whole The resultant of these is reflected in the blood pressure readings, which vary from individual to individual depending upon the degree to which each factor may be operative. Those asymptomatic individuals whose resultant hypothetic "*sphygmostat*" (blood pressure regulator) is set *at a low level* may be regarded as *normal variants*, while those whose low "sphygmostatic" level is productive of symptoms, may be regarded as a constitutionally *abnormal type* The basic explanation, however, remains unknown

SECONDARY HYPOTENSION

This group is extremely heterogeneous, since hypotension is merely a sign, only one part of a *syndrome*, symptom complex, or disease entity Hypotension in this connection is merely secondary to mechanisms resulting in the genesis of the syndrome For example, the hypotension that accompanies shock is an integral part of that syndrome but gives no indication as to the mechanism or etiologic factors which may have produced it.

Acute Secondary Hypotensive State. This term refers to a sudden precipitous fall in blood

pressure frequently associated with syncope or semicomatose, shock, or shocklike states. The condition may be quickly reversible or lingering. There are many syndromes of which acute hypotension is a part.

Shock. Shock is an example of an acute hypotensive state. There are several categories of shock or shocklike states, including surgical, traumatic, metabolic, and cardiogenic.

It is interesting to note the frequency of occurrence of postoperative adrenal cortical insufficiency. "One out of 300 patients subjected to surgery exhibit some form of adrenal cortical insufficiency." Cases are reported of acute adrenal cortical insufficiency in which persistent hypotension and shocklike states develop during surgery and immediately postoperatively, with severe peripheral collapse and failure to respond to intravenously administered blood and serum, electrolyte therapy, and vasoconstrictors. These patients, however, respond promptly to intravenous hydrocortisone therapy. The mechanism whereby hydrocortisone produces such prompt therapeutic response is not known. It is thought to be the result of the potentiating effect upon vasoconstrictor agents or the direct effect upon the peripheral blood vessels (Adams et al.)

Cardiogenic Shock. The mechanism and classification of *cardiogenic shock* in the following paragraphs are largely taken from reviews of this subject (Sampson).

The figure 10 per cent is generally quoted to be the incidence of shock accompanying all cases of *myocardial infarction.* Vasopressor drugs have been credited with reducing the mortality in those shock patients if treatment is instituted within 3 hr (Griffith et al).

"Cardiogenic shock" (shock of cardiac origin) is characterized by an acute precipitous fall in the blood pressure and by signs of acute circulatory collapse, viz., weak rapid pulse, pallor or cyanosis, sweating, anxiousness, and restlessness. Hypotensive episodes such as these are due primarily to myocardial failure to maintain adequate blood flow Concomitantly, there is peripheral vascular failure The mechanism in myocardial infarction, the most common cause of cardiogenic shock, is primarily *a sudden reduction in left ventricular output due to a direct loss of functioning myocardium* Secondarily, there is *an autonomic reflex causing pooling of the blood in the viscera and dependent portions of the body* (Sampson)

Following extensive myocardial infarction, there is *a reduction in stroke volume,* which may result in congestive heart failure and accentuation of the shocklike state Vasoconstrictor mechanisms (arterial) fail to maintain normal blood pressure, and the reduced "head of pressure" is insufficient to supply the myocardium, brain, and kidneys with adequate oxygen.

Some significant data have resulted from the production of shock experimentally in dogs, which if applicable to human beings, help explain the pathophysiology of shock accompanying myocardial infarction (Corday et al). It has been shown that following experimental shock there is reduced coronary blood flow. Furthermore, the ballooning of the ischemic myocardium following ligation of the coronary arteries seems to become exaggerated when the blood pressure is lowered by bleeding In order to maintain adequate oxygen supply to the myocardium and to prevent irreversible myocardial damage, the pressure within the coronary arteries must be maintained at adequate levels. The rapid restoration and maintenance of the systemic blood pressures sufficient to provide adequate coronary artery blood pressure levels is one goal in the treatment of shock that may accompany acute myocardial infarction.

In addition to the above-mentioned *myocardial hypoxia* resulting from acute hypotension of cardiogenic shock, *cerebral hypoxia* may be a factor in the ultimate prognosis of patients having cerebral as well as coronary arteriosclerosis. The effect of artificially induced hypotension upon the cerebral hemodynamics of 12 individuals over 50 years of age with evidence of cerebral vascular disease and hypertension has been studied using tetraethylammonium chloride (Bessman et al.).

No quantitative changes were noted in the cerebral hemodynamics, but 80 per cent of the patients manifested subjective and objective signs ordinarily attributed to cerebral anoxia during the period of hypotension. This apparent discrepancy was explained by vasodilatation occurring in less diseased vessels at the expense of the severely arteriosclerotic vessels and producing a "stagnant anoxia" not measurable by current techniques The hypoxia thus would occur in those areas which had a barely adequate oxygen supply prior to the time hypotension

If the shock persists, *irreversible shock* ensues The duration of this interval before irreversible shock develops may be from 1 to 4 hr. Small-vessel thromboses, especially in the lungs, as a result of "hypercoagulability and stagnant flow" or/and the release of some vasodepressor substance (VDM) coming from hypoxic liver tissue (Shorr et al) may explain irreversible shock. The addition of heparin to vasopressor infusions has been reported to improve the survival rate (Griffith)

Cardiac conditions other than myocardial infarction may produce cardiogenic shock and be associated with sudden reduction in cardiac output, they are cardiac tamponade (traumatic or ruptured dissecting aneurysm) and supraventricular or ventricular tachycardia. Ventricular fibrillation caused by electric shock results in sudden fall in cardiac output and sudden death. Acute myocarditis, Stokes-Adams syndrome, ventricular standstill, ball-valve thrombus, or pedunculated myxomas may cause shocklike states with acute hypotensive episodes, as a result of ventricular asystoles or ineffective ventricular contractions

Miscellaneous Medical Entities. The following entities may produce *shocklike* states and occasionally result in myocardial infarction and cardiac decompensation·

1 *Hemorrhage* due to gastrointestinal bleeding, e g , bleeding peptic ulcer
2. *Reduction in circulating blood volume* due to dehydration, vomiting, or diarrhea with associated sodium and potassium imbalance
3 *Cerebral accidents*—occlusion of cerebral arteries or hemorrhage
4 *Pulmonary embolism* and infarction
5 *Peripheral vascular collapse as a result of*
   a Anaphylaxis or anaphylactoid reactions resulting from allergies to horse *serum or egg* albumin, and in *favism* (the liberation of histamine produces *arteriolar* dilatation with loss of fluid into the interstitial tissues as a result of increased capillary permeability with consequent reduction in the circulating blood volume)
   b. Gram-negative bacterial septicemias
   c. Parenteral drug sensitivities (penicillin, histamine, mercury, arsenic, aminophylline, barbiturates, Pronestyl, quinidine, veratrum, or chlorpromazine)
   d Acute adrenal insufficiency resulting from meningococcemia (Waterhouse-Fridrichsen syndrome)

[illegible]

An acute drop in arterial blood pressure levels may result from a *hypersensitive carotid sinus.* Basically, the hypotension results from vagal stimulation such as occurs in pressure on the eyeball (oculovagal reflex), paracentesis (peritoneal reflex), and thoracentesis [illegible]vagal reflex). The results are slowing [illegible] and [illegible] cerebral hypoxia. Treatment [illegible]ninistration of *atropine* by mouth, 05 mg three times a day, in order to cause paralysis of the vagal nerve endings

Acute Infectious Diseases. Cholera, diphtheria, pneumonia, scarlet fever, typhoid, typhus, and epidemic hemorrhagic fever have caused acute hypotensive episodes which may persist for long intervals Particularly, gram-negative *bacteremias* and other *acute fulminating infections* may result in severe hypotensive states secondary to peripheral vascular collapse. Blood or plasma transfusions are of little value in their treatment, since there is no evidence of hemoconcentration or decreased blood volume It is thought that the peripheral vasodilatation resulting from a decrease in peripheral vascular tone is secondary to depression of vasomotor *centers* in the central nervous system In addition to peripheral vascular failure, acute toxic myocarditis (streptococcal infections, acute glomerulonephritis, acute rheumatic fever, or diphtheria) may complicate the picture, leading to severe shock and death In *typhus fever*, characteristically, the patients suffer severe hypotensive periods followed by renal insufficiency with accompanying diminished urea clearance, increase of blood urea nitrogen, and oliguria. In *epidemic hemorrhagic fever* (*Manchurian fever*)—a disease thought to be due to a virus—fever, prostration, vomiting, proteinuria, and shock with renal failure may develop

The disease attracted wide attention during the Korean War in 1951 among United Nations troops Early death due to shock, generally associated with retroperitoneal hemorrhage and petechiae in the viscera, occurred in 13 cases. The hypotensive *phase* was associated with reduced blood volume and marked elevation in the hematocrit, presumably due to loss of plasma into the tissue [illegible]

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   d. *Acute adrenal insufficiency* resulting from meningococcemia (Waterhouse-Friderichsen syndrome)
   e. *Epinephrine and l-norepinephrine* deficiencies following removal of adrenal tumors

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The disease attracted wide attention during the Korean War in 1951 among United Nations troops. Early death due to shock, generally associated with retroperitoneal *hemorrhage* and petechiae in the viscera, occurred in 13 cases The hypotensive phase was associated with reduced blood volume and marked elevation in the hematocrit, presumably due to loss of plasma into the tissue spa-

The *treatment* is general and supportive, and specific therapy is employed depending upon the etiologic agent. Digitalis is indicated in severe cardiac decompensation; intravenous l-norepinephrine is used to combat the severe peripheral vascular dilatation.

Hypotensive Drugs and Anesthetics. Drugs used in the treatment of hypotension may cause acute hypotensive episodes with syncope.

Ganglionic blocking agents (tetraethylammonium chloride and hexamethonium) may result in acute postural hypotension with tachycardia. The ganglionic blockade causes decreased peripheral arterial resistance.

Centrally acting *sympatholytic agents* (1-hydrazinophthalazine–*Apresoline*) may likewise cause pooling of the blood and venous congestion in dependent portions of the body associated with loss of tone in the peripheral vascular bed and consequent hypotension and syncope.

Relatively severe acute hypotensive episodes may occur with the use of *spinal anesthesia*, deep inhalation anesthesia, and tribromoethanol (*Avertin*).

Hysteria. Severe emotional reactions may result in an acute hypotensive episode with *syncope*. This generally occurs in individuals with marked vasomotor instability. Horror at witnessing a gruesome spectacle, news of sudden death, the sight of blood, fear of venipuncture, and the marked vasodepression when sensitive organs are injured (testicles, incising a boil, inserting a canula into an artery, stimulating sciatic or ulnar nerves) may precipitate fainting. In anticipation of the threatened "faint," one notes marked pallor, anxiousness, sweating, weakness, and nausea. The blood pressure falls acutely and is associated with tachycardia. Particularly in the upright position, there is pooling of the blood in the lower extremities, secondary to reflex muscular vasodilatation There is reduced cerebral blood flow with consequent cerebral hypoxia, and syncope ensues Treatment consists of lying down or bending the head and trunk and drawing up the knees.

Cough Syncope and Reduced Venous Return to the Heart. Severe paroxysms of cough cause a rise in the intrathoracic pressure, which reduces the venous return (Valsalva maneuver), thus reducing cardiac output and consequently lowering the blood pressure, with attendant syncope and, occasionally, convulsi[ve] seizures. Treatment is directed against increa[s]ing the intrathoracic pressure by avoiding li[ft]ing or pushing heavy objects or straining [at] stool and eliminating the pulmonary conditi[on] causing the cough.

Reduced venous return to the heart m[ay] produce fainting in *pregnant women*, in who[m] the dorsal recumbent position, for prolong[ed] periods, causes obstruction of the inferior ve[na] cava through pressure exerted by the hea[vy] gravid uterus. The reduced venous return [to] the heart subsequent to the pooling of blo[od] which occurs in large *varicose veins* and veno[us] angiomas of the legs frequently results [in] lowering of the blood pressure.

Effort Syncope Due to Primary Pulmona[ry] Hypertension. Despite the normal oxygen sa[tu]ration of the blood which prevails in this d[is]ease and consequent absence of cerebral h[y]poxia, syncope occurs frequently. Strenuo[us] effort or emotional upset may cause an ac[ute] drop in blood pressure. This may be explain[ed] by the rise in the pulmonary arterial pressu[re] which causes stimulation of the nerve endi[ngs] in the pulmonary artery, with production o[f a] vagal reflex and a sudden fall in blood press[ure] with bradycardia.

Hypoxia. In *anemic states*, there is increa[sed] cardiac output to compensate for the redu[ced] oxygen-carrying capacity of the blood. [The] decreased peripheral resistance secondary [to] reflex arteriolar dilatation accompanying sev[ere] effort may result in syncope, in view of [the] existing hypoxia in the brain which acco[m]panies the anemia. Severe exertion in ot[her] hypoxic states, such as those which occur [at] *high altitudes* and *in congenital heart lesi[ons]* (tetralogy of Fallot, congenital atresia of [the] tricuspid valve), may result in sudden sev[ere] hypotension and syncope

Strenuous Exercise. In severe exercise th[ere] is a redistribution in the circulating bl[ood] volume. The total vascular bed is increa[sed] because of peripheral vasodilatation in [the] muscles, particularly of the legs. This redu[ces] the "effective circulating volume of the bloo[d,] producing hypotension, cerebral hypoxia, [and] syncope In the *superior caval syndrome*, sev[ere] effort or straining may result in sudden dist[en]tion of the cerebral veins, with resultant s[yn]cope Cerebral stagnation and hypoxia are [the] physiologi...

Chronic Valvular Disease of the Heart. In *aortic stenosis* associated with left ventricular hypertrophy, dizziness or syncope may result when sudden demands (strenuous effort) upon the cardiac output cannot be met because of the obstruction to blood flow by the stenotic valve, which prevents significant increase in the left ventricular stroke volume. Cerebral hypoxia may thus result, producing dizziness or faintness Similarly, in mitral, pulmonic, or tricuspid stenosis, severe dizziness or fainting may occur In these latter conditions, low blood pressures, occasionally approaching shock level, are found occasionally following exercise, presumably as a result of the failure of ventricular output to compensate for the increased demands resulting from the peripheral vasodilatation which occurs during strenuous exercise

Hypotension in Aviation. The sudden changes in atmospheric pressure to which an aviator may be subjected occasionally result in acute hypotensive episodes with syncope. *At extremely low atmospheric pressures,* the decreased atmospheric oxygen may result in dizziness and giddiness Furthermore, sudden *rapid acceleration* or *rapid deceleration* may cause "*black-outs*" at high altitudes Additionally, *air emboli,* with syncope and occasionally sudden death, may result from the release of nitrogen from the blood as a result of a sudden fall in the atmospheric pressure

Heat Exhaustion. Heat exhaustion is the result of acute peripheral vascular collapse In hot environments, there is an increased need for circulating blood in the skin, muscles, and brain

The environmental factors are temperature, humidity, and wind velocity There are increased circulatory demands of the skin to permit the dissipation of heat from the body via the blood vessels of the skin and via the sweat glands, which themselves require increased blood supply The sudden decrease in the peripheral vascular tone and the fall in cardiac output result in the failure of the body to maintain a peripheral blood supply adequate to satisfy the increased circulatory requirements The presence of a sodium deficiency may be predisposing

Nausea, vomiting, headaches, and syncope are the accompaniments The prognosis is good. Treatment consists of rest, increased salt intake, and attention to any cardiovascular disease that may be underlying

Heat Stroke. Heat stroke results from the failure of the sweat mechanism. There is a breakdown of temperature regulation because of the cessation of sweating, with elevation of body temperature up to 105°F. Mental confusion, staggering gait, headache, delirium, and coma characterize this syndrome. Secondary vasomotor shock and death occur if treatment is not immediately administered. The basic therapy consists of lowering the temperature to safe limits (if possible 102°F or below). This is done by immersing the patient in cool or iced baths or by spraying him with water, using a fan to produce rapid evaporation (Darling)

CHRONIC HYPOTENSION

In this category are included those patients who may suffer from repeated bouts of intermittent hypotensive crises (orthostatic hypotension) or protracted hypotensive states (Addison's disease, Simmonds's disease). Chronic hypotensive states, in contradistinction to the acute hypotensive states, do not require heroic treatment or immediate remedial procedures, as they are not critical or inimicable to the existence of the *individual.*

Primary "Idiopathic Orthostatic Hypotension." This condition was originally described by Bradbury and Eggleston (1925). The literature was reviewed in 1954 and the subject discussed; only about 50 cases had been reported until that time (Benestad et al). One new case was reported by those authors. The disease occurs most commonly in middle-aged males and is characterized by diastolic and systolic hypotension upon assuming the upright position, anhidrosis, and impotence (East et al). *The pulse rate, however, is not affected.* The term "idiopathic orthostatic hypotension" is adopted by Benestad, to distinguish from orthostatic hypotension, which is symptomatic of other disease states It was observed that in addition to the triad mentioned above, miosis and psychic disturbances were present. Electroencephalographic tracings demonstrated *cerebral ischemia in the* upright position. No changes were noted in electrocardiogram, and the heart rate remained unchanged The glomerular filtration rate and tubular reabsorption were diminished in the upright position Following syncope, there was an increase in a number of young leucocytes in the peripheral

blood. The urinary excretion of norepinephrine was decreased. This disease affected both the sympathetic and parasympathetic nervous systems. The usual sympathetic reflex, which causes vasoconstriction and compensates for the normal pooling of blood in the lower extremities upon standing, is absent. There is no apparent congestion of the lower extremities in these cases, while there is a definite decrease in venous return. Indicative of the disturbance in the parasympathetic nervous system is the fact that vagal stimuli (such as pressure upon the carotid sinus) fail to produce a response Although the etiology is unknown, it is most probable that idiopathic orthostatic hypotension is the result of some pathologic lesion in the hypothalamus affecting the autonomic nervous system It is postulated also that a hyposensitive carotid sinus or the failure of the adrenal glands to produce norepinephrine may be the physiologic mechanism in the production of this syndrome. The presence of leucocytosis may be an indication that cerebral hypoxia is providing the stimulus to the hypothalamus, which is thought to control the regulation of production of leucocytes.

Treatment thus far has been ineffectual in preventing idiopathic orthostatic hypotension The use of abdominal corsets and elastic bandages on the lower extremities has had poor success. Although no treatment based upon the etiology has been developed, symptomatic improvement by *"head-up" treatment*, in which the bed is raised during the night, and particularly by the use of *ephedrine* orally administered, has resulted in raised systolic and diastolic blood pressures The disease is progressive and the prognosis poor

Secondary (Chronic) Orthostatic Hypotension. Chronic orthostatic hypotension is characterized by fall in blood pressure upon assuming an upright position from the recumbent or squatting position. Weakness, dizziness, pallor, sweating, abdominal discomfort, and blurred vision may result. Occasionally, severely hypotensive episodes with syncope may ensue In most instances, except for idiopathic orthostatic hypotension discussed above, the condition is secondary to other disease states.

POSTSYMPATHECTOMY SYNDROME. In assuming the upright position following splanchnicectomy (generally performed in the treatment of essential hypertension), there is pooling of blood in the splanchnic area and in the lower extremities. The severence of the thoracolumbar sympathetic chain prevents the reflex arteriolar constriction which would otherwise occur. Consequently, there is a marked reduction in the circulating blood volume. Dizziness, dyspnea, and headache are characteristic symptoms. The condition generally lasts but a few months. The treatment consists of wearing an abdominal binder and elastic stockings.

CENTRAL NERVOUS SYSTEM DISORDERS In tabes dorsalis, syringomyelia, subacute combined degeneration, amyotrophic lateral sclerosis, encephalitis, and parkinsonism, there is an interruption of the sympathetic pathways depending upon the site of the pathologic lesion (hypothalamus, medulla, or spinal cord) and resulting in the loss of vasomotor tone, particularly arteriolar contraction. An additional factor is the pooling of blood in the splanchnic area and the lower extremities upon assuming the upright or sitting position, as a result of poor venous return secondary to the flaccid paralysis (loss of muscle tone) which accompanies these diseases. Treatment consists of the avoidance of overeating, sufficiently long periods of rest following meals, and the use of abdominal binders and elastic stockings.

CHRONIC DEBILITATING DISORDERS Protracted periods of bed rest occasioned by *extensive surgical procedures, severe acute infectious diseases* with prolonged convalescence, *chronic infectious diseases* (pulmonary tuberculosis), *rheumatoid arthritis, malnutrition*, etc, may result in orthostatic hypotension when these patients become ambulatory. Poor muscle tone results in the pooling of blood in the dependent portions so that there is reduced venous return to the heart In *primary atypical (viral) pneumonia*, there is thought to be loss of vasomotor tone owing to interference with the sympathetic vasomotor constrictor mechanism with reduced circulating blood volume resulting in postural hypotension Other chronic debilitating diseases frequently referred to in the literature as associated with hypotension are chronic alcoholism, parasitic infestations, lipoid nephrosis, poisonings, anorexia nervosa, ulcerative colitis, and carcinomatosis. Severe *opium poisoning* results in pronounced fall in the blood pressure, with tachycardia, pulmonary edema, and occasionally convulsive seiz-

ures. In less severe poisoning, nausea, vomiting, pruritus, drowsiness, sleep, and coma ensue.

Endocrinopathies. Chronic hypotension is found in Addison's disease, Simmonds's disease, hypothyroidism, and acromegaly.

In *Addison's disease,* symptoms of dyspnea and palpitation upon exertion do occur, but cardiac failure is uncommon The systolic blood pressures may vary from 80 to 100 mm Hg, and the diastolic may vary from 50 to 65 mm Hg Electrocardiographic changes are present but not typical. Low voltage, prolongation of the QRS interval, and inverted T-wave changes may be found. This may or may not reflect myocardial lesions and may represent the functional status of the adrenal cortex (electrolyte balance, circulating blood volume, etc) The heart size radiographically is smaller than normal, probably secondary to the loss of sodium and consequent loss of body fluids resulting in decreased circulating blood volume Severe shock (*Addisonian crises*) with severe hypotension, hemoconcentration, low sodium, high potassium, elevated blood urea nitrogen (renal failure due to low filtration pressure) may develop in a few hours when the individual is exposed to stressful situations such as childbirth, surgical procedures, severe upper respiratory infections, or gastrointestinal infections. These crises are thought to be due to failure of the individual to respond with increased adrenal cortical secretions and to further derangement of the electrolytic equilibrium owing to the loss of sodium and water.

The cardiovascular manifestations of *hypothyroidism* are due to the *myxedematous,* flabby myocardium, which results in reduced stroke volume and often, but not always, in lowering of the blood pressure The pulse rate remains unchanged The electrocardiogram may show T-wave inversions, low voltage, and prolongation of the QRS interval. Variability in a blood pressure cannot be explained, although cardiac output is reduced and circulation times are increased in most instances.

In far-advanced *acromegaly* and in *Simmonds's disease* (panhypopituitarism), hypotension exaggerated by postural changes is a frequent finding associated with syncopal attacks.

Chronic Cardiac Disorders. The following conditions may be associated with chronic hypotension: myocardial amyloidosis, fibroelastosis, constrictive pericarditis or pericardial effusion, and aortic stenosis. Occasionally, after severe myocardial infarction with shock, the hypotension may persist, even when shock has been successfully treated and overcome. This is apparently because of the persistence of reduced peripheral vascular resistance in view of a lack of reduction in cardiac output.

In *congestive heart failure,* the blood pressure is not lowered despite decreased cardiac output The probable explanation is a compensatory, peripheral vascular constriction.

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ABNORMAL CAROTID SINUS REFLEX

A variety of causes and predisposing factors are responsible for *increased sensitivity* of the carotid sinus. *Local causes* include inflammation or enlarged lymph nodes, tumor masses, adhesions, or scar tissue in the neck. Aneurysmal dilatation or arteriosclerotic alterations within the sinus itself belong to this category. Syphilis, brain tumors, and skull fractures may be responsible for hypersensitivity of the central connections in the medulla. Irritability of the efferent arc of the reflex may arise from arteriosclerosis, hypertension, and coronary artery disease. *Digitalis* is an important sensitizing agent of the peripheral vagal endings in the heart. Age and sex are contributing factors. The carotid sinus syndrome is common in the male, particularly the aged. The menopause also predisposes to sensitivity of the carotid sinus reflex. Neurotically conditioned individuals are particularly vulnerable. Other predisposing or contributing causes include nutritional deficiency, particularly of thiamine; biliary tract and esophageal disease, contralateral carotid artery thrombosis, and hypoxemic or hypoglycemic states. The erect posture and certain neck movements are important precipitating factors. In susceptible individuals, the carotid sinus syndrome may be set in motion by turning the head suddenly to one side during the process of shaving, or by stooping, coughing, or straining. Chiropractic manipulation and trauma to the neck may be responsible for attacks. Any surgical or anesthetic procedure in which the patient is maintained in an upright posture, and the neck is hyperextended or manipulated, sensitizes the reflex.

Depending on the efferent pathway involved, three types of carotid sinus syncope have been described (Weiss, S.). The first, or *vagal type*, is characterized by marked slowing of the heart, varying from sinus bradycardia to complete asystole depending on the degree of vagal activity. From its inhibitory effect on the AV conduction system, all types of AV block may develop. Occasionally, atrial flutter or fibrillation has been observed. The cerebral symptoms observed in this type result primarily from slowing of the heart and the consequent fall in blood pressure. A hypersensitive carotid sinus reflex may form the basis for a Stokes-Adams syndrome.

The second, or *depressor type* of carotid sinus syncope, is uncommon and is characterized by a sudden drop in arterial pressure without significant slowing of the heart. Cerebral symptoms are secondary to peripheral vasodilatation.

The third, or purely *cerebral type* occurs without either slowing of the heart or fall in blood pressure. The mechanism of this type is the least understood. It has been suggested that certain areas of the brain are stimulated. A more logical explanation is that actual impairment of the carotid flow to the brain is the underlying cause.

Clinically, the carotid sinus syndrome is usually a combination of two or more types. A fourth, or *mixed, type* should therefore be included in the classification. A common type *is a combination of the vagal and depressor syndrome.*

The *symptoms* observed in the carotid sinus syndrome follow no fixed pattern. The onset may be ushered in with prodromal symptoms consisting of visual blurring, scotomas, unsteadiness, dizziness, weakness, lightheadedness, nausea, epigastric distress, and tinnitus. Paresthesias of the face or extremities occur on the side contralateral to the affected sinus because of the commonly encountered decussation of nervous pathways. Syncope follows and is of short duration. The muscles are flaccid, and there is a facial pallor followed by a flush and diaphoresis. Breathing is slow and shallow. Convulsions, in some cases unilateral, are usually associated with syncope. In the cerebral type, however, convulsions may appear independently of loss of consciousness. It should be emphasized that in many individuals with the carotid sinus syndrome, mild symptoms, without syncope or convulsions, are common.

The diagnosis of carotid sinus syndrome is frequently missed. It should be suspected in any patient who presents a history of unexplained dizziness, weakness, syncope, convulsions, or related manifestations. In the *differential diagnosis*, the following conditions should be considered: epilepsy, cataplexy, hypoglycemia, Ménière's disease and vertigo, hyperventilation syndrome, hysteria, heart block, cardiac arrhythmias and paroxysmal tachycardias, postural hypotension, and vasovagal disorders.

Reproduction of the exact symptoms by

The carotid sinus syndrome

JACOB J. SILVERMAN AND SIEGFRIED SALOMON

Approximately a century and a half ago Parry first observed that pressure on the neck along the course of the carotid artery gave rise to a slowing of the heart. The relationship between the carotid artery and syncope, however, had been known since ancient times. It is now known that certain mammals, notably horses and goats, depend entirely on the carotids for their cerebral blood supply, as the vertebral arteries are poorly developed.

THE CAROTID SINUS

The carotid sinus is a short, thin-walled, slightly bulbous dilatation of the common carotid artery, located bilaterally near its bifurcation into the internal and external carotid arteries. Occasionally the sinus dilatation involves a portion of the internal carotid artery as well The walls of the sinus contain an extensive nervous network of highly specialized myelinated sensory end organs (*pressoreceptors*), which are most numerous between the connective tissue fibers within the tunica adventitia. This unique anatomic arrangement permits easy stimulation when the arterial wall is stretched Similar receptors are found in the arch of the aorta, in the bronchioles, and in various blood vessels throughout the body. The afferent arc of the carotid sinus reflex originates in the specialized receptor cells of the sinus wall to form the *carotid sinus nerve* ("sinus nerve of Hering," "intercarotid nerve of de Castro"), which in turn ascends between the internal and external carotid arteries to join the glossopharyngeal nerve. Fibers of the afferent arc terminate centrally in the cardioregulatory, vasomotor, and other autonomic centers in the medulla. The final efferent pathways are by way of the vagal and cervical sympathetic connections (Part 1, Chap. 14).

THE CAROTID SINUS REFLEX

The carotid sinus reflex is an important physiologic mechanism for the maintenance of a uniform blood pressure and an adequate blood supply to the brain. It is particularly important in states of stress. A sudden rise in arterial pressure stretches the wall of the carotid sinus Since the receptor end organs of the carotid sinus are stimulated by stretching of the sinus wall, a sudden rise in intraarterial pressure initiates a series of cardiovascular reflexes and thereby causes a prompt lowering of the blood pressure and a slowing of the heart Conversely, a decline in intrasinal pressure reflexly initiates vasoconstriction and tachycardia. The normal function of the carotid sinus reflex is reflected chiefly in its tonic effect on the cardiovascular system Indirectly, however, it is capable of widespread reactions through its connections with a number of autonomic centers in the medulla. Hence, activity of the carotid sinus may influence respiration, skeletal muscle and bladder tone, gastrointestinal activity, and the secretion of epinephrine. Because of its close anatomic relationship, the carotid body is sometimes confused with the carotid sinus. The carotid body, however, is a *chemoreceptor* organ and is stimulated by hypoxia, increased carbon dioxide tension, and a number of drugs Its principal action is related to respiration, but through sympathetic activity, it also influences the blood pressure and pulse rate (Part 2, Chap 12).

3

Vasovagal syncope

JACOB J. SILVERMAN AND SIEGFRIED SALOMON

A common form of syncope is vasovagal syncope, or *simple fainting* It occurs more frequently than all other types of syncope combined Attacks always occur in the standing or sitting position and are relieved by recumbency Fainting as a result of *prolonged standing* is a familiar example of vasovagal syncope An ordinary venipuncture may provoke an attack in a robust individual. Most attacks are benign In the aged or in the presence of organic heart disease, however, this syndrome can be fatal In the enthusiasm to encourage ambulation, hospital patients are sometimes forcibly propped up in a wheel chair or armchair Such patients, particularly if debilitated, may easily develop vasovagal syncope If recumbency is not quickly established in these patients, death may promptly follow Similarly, the upright posture in certain operative procedures may be responsible for a number of unexplained anesthesia deaths

The syndrome of vasovagal syncope is a reflex disturbance conditioned by many factors Fear, anxiety, and pain, either imaginary or real, are common predisposing causes The following are some of the more important cardiovascular situations in which the vasovagal syndrome may be observed.

1 Prolonged recumbency and convalescent states, especially in elderly persons

2 Peripheral circulatory failure

3 Any tachycardia with a ventricular rate of over 160 per minute

4 Embolic or infarction states

5 Aortic valvular disease

6 Sudden visceral catastrophes (acute pancreatitis)

7 Ordinary venesection or paracentesis

8. Loss of blood, internal or external

9 Electrolytic disturbances and dehydration

10 Hypoglycemic states

11. Hypertensive encephalopathy

12 Localized cerebrovascular disease

13 Reflex hyperventilation state

14. Side reaction to drugs (ganglionic blocking agents)

The mechanism of vasovagal syncope is complicated and not entirely understood. It occurs under such a wide variety of circumstances that it is probable that multiple reflexes or mechanisms are involved. It is interesting that between attacks, patients with this syndrome almost invariably demonstrate no abnormalities. The important role of emotional influences has been discussed in detail by Engel (1950). In biologic terms, loss of consciousness as a reaction to fear or danger may represent a primitive protective response to conserve the total organism "Sham death" is a lifesaving device in certain animals when exposed to overwhelming danger.

During an attack of vasovagal syncope, many features of shock are present The basic disturbance may well represent a hypersensitivity of the splanchnic vascular system. As a result of this disturbance, blood accumulates in the dilated splanchnic vessels, cardiac output drops, and there is a peripheral circulatory collapse The elevation in diastolic pressure and rise in pulse rate observed just before the faint are obviously due to a compensatory mechanism. When this mechanism fails, the blood pressure abruptly falls and syncope develops. The slow heart rate observed during the stage of syncope is a result of increased

applying pressure over the carotid sinus is the only sure way of confirming the diagnosis. It should be emphasized that artificial stimulation of the carotid sinus in clinically normal individuals is capable of producing a wide variety of symptoms and electrocardiographic changes, including asystole. To repeat, if the symptoms produced by artificial stimulation of the carotid sinus are not an exact reproduction of those experienced during attacks, the diagnosis of a hypersensitive carotid sinus syndrome should be doubted or discarded.

Artificial testing for carotid sinus sensitivity may be hazardous and requires careful attention to certain details. The patient should be seated on the edge of the examining table with the head slightly extended. An attempt should be made to identify the bulb of the carotid sinus. Although not always easily located, the landmark is the angle between the larynx and the anterior margin of the sternocleidomastoid muscle at the level of the thyroid cartilage. After the sinus is located, it is manually compressed against the cervical spine and mildly massaged for not more than 30 sec, unless the diagnosis is established earlier. If an insignificant response is obtained, multiple areas are stimulated in order to eliminate anatomic variations of the location of the carotid sinus. The right side of the neck is first stimulated, since this side is usually the more sensitive. However, if no response is obtained on the right side, the procedure is repeated on the left. Under no circumstances should *both* carotid sinuses be tested simultaneously. With the aid of an assistant, the blood pressure and pulse rate are recorded. A continuous electrocardiographic tracing is valuable. If an attack is induced, it is often desirable to repeat the test after the patient has been atropinized. In doubtful cases, it may be necessary to repeat the test after novocainization of the sinus.

Testing for carotid sinus sensitivity is not without risk, particularly in the aged. Serious neurologic complications have been reported following carotid sinus stimulation. Recovery from spontaneous and induced syncopal attacks, however, is usually prompt and uneventful.

Therapy. Therapy of the carotid sinus syndrome will depend largely upon the frequency and nature of attacks, as well as on the predisposing causes. Immediate treatment usually consists in placing the patient in a comfortable horizontal position with the head lowered. All tight clothing should be loosened and any pressure around the neck relieved. Vigorous antishock treatment is rarely necessary, but epinephrine is the drug of choice if there are signs of vasomotor collapse or if the heart rate is extremely slow.

Any localized or potential source of pressure in the region of the carotid sinus should be investigated. Avoidance of a tight or high collar may be curative. Inflamed lymph glands or tumors adjacent to the carotid sinus should be appropriately treated.

Unilateral surgical section of the nerve or *denervation of the carotid sinus* is occasionally necessary if attacks occur at frequent intervals and are disabling. As a last resort, if sinus denervation fails, section of the intracranial portion of the glossopharyngeal nerve should be considered. In recent years, a promising number of patients with the carotid sinus syndrome have been treated successfully by x-ray irradiation of the sinus.

For the prevention of the vagal or cardioinhibitory reflexes, cholinergic blocking drugs are prescribed. These include atropine, belladonna, scopolamine, and *Banthine.* Sympathomimetic drugs are also valuable, since they increase the excitability of the myocardium, counteract ventricular slowing, and thus prevent cardiac arrest; epinephrine, ephedrine, *Isuprel, Paredrine, Benzedrine,* and *Neo-synephrine* belong to this category. In the group of cases with the predominant vasodilator reflex (the vasodepressor type), the sympathomimetic drugs, particularly epinephrine, are indicated. In the absence of cardiac slowing, the cholinergic blocking drugs are not used. Drug therapy in the cerebral type of reflex is of little or no value.

Wherever possible, attempts should be made to improve the patient's general physical and mental health. Any metabolic disturbance or nutritional deficiency, particularly thiamine deficiency, should be corrected. Tobacco, coffee, digitalis, insulin, and morphine may be predisposing sensitizing agents. Any related reflex disturbance, such as biliary tract disease, should be corrected or eliminated, if possible. For many patients, a cure is not obtainable, and continuous prophylactic administration of atropine, alone or in combination with a sympathomimetic drug, may be necessary.

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vagus tone and is a secondary effect. That the cardiac slowing is not causative but secondary can be demonstrated by the experimental administration of atropine. This drug, in doses of 1 or 2 mg, will abolish the slow heart rate and heart block but fails to prevent loss of consciousness.

The *symptoms* of vasovagal syncope are brief and dramatic. The onset takes place within a matter of seconds to a few minutes. The earliest symptom is a feeling of *apprehension*, followed by *muscular weakness*, *epigastric distress* with *nausea* or *retching*, *sweating*, *sighing type of respiration* or yawning, *tremors*, and finally *collapse*. Precordial pain and a sense of rotation are conspicuously absent. There are many gradations of vasovagal syncope; in the *mild type*, symptoms are variable and minimal. An important feature of the syndrome is the relief obtained by the recumbent posture Recovery is usually prompt During a *severe attack*, when the patient is deeply unconscious, a flurry of excitement surrounds the event. The patient in fact may appear to be dying. The face is frightfully pale and drenched with sweat. The hands are cold and moist; the radial pulse is imperceptible. Respirations follow no set pattern; they may be slow, deep, or shallow. The pupils are dilated and the reflexes may be lost. The muscles are flaccid and limp, occasional clonic muscular movements are seen

Following the attack, which is usually over within a few minutes, patients complain of muscular weakness and poor coordination, and are often left with a severe headache lasting for several hours. As a result of the fall they may have suffered from a serious laceration, a dislocation, or a fracture.

The immediate *management* of vasovagal syncope ordinarily is simple The patient is placed in a horizontal position with *the head lowered*. Spontaneous recovery is the rule All tight clothing is loosened. After consciousness has returned, it is wise to have the patient continue to lie flat until normal muscular power has returned. If he is permitted to sit up too quickly, symptoms are apt to recur Exercising the legs in a recumbent position is desirable. In prolonged attacks, parenteral administration of atropine and epinephrine occasionally may be indicated. The patient should always be examined for blood loss or serious injury. Rarely, if cardiac arrest supervenes, artificial respiration and cardiac massage should be attempted, or if a cardiac pacemaker is available, external electric stimulation is administered.

Vasovagal syncope tends to be repetitive, an attempt therefore should always be made to treat or remove the predisposing cause Any metabolic, nutritional, or electrolytic disturbance should be corrected. An abdominal support or a corset may be valuable in patients with flabby musculature. Prolonged standing or maintenance of an erect posture in susceptible individuals should be avoided Obviously, if there are profound emotional disturbances, the patient may require intensive psychiatric treatment.

4

Shock

Shock in General

EDWARD D. FRANK

Metabolic Aspects of Shock

STANLEY LEVENSON AND ALBERT EINHEBER

SHOCK IN GENERAL

Shock is a circulatory disorder in which the basic defect is *an acute persisting deficiency of peripheral blood flow*. Progressive and widespread deterioration of function is the inevitable result. The rate and extent of the deterioration depend upon the severity and duration of the deficiency in flow. Since lethal tissue damage due to shock may occur insidiously within minutes or hours, immediate recognition of the state of shock is essential, so that aggressive and effective treatment may be instituted.

PATHOPHYSIOLOGY

By definition, shock implies trauma. But the trauma need not be overt physical destruction of tissue. It may also be *chemical, as from a drug or a bacterial toxin*. Except for infection, the initial blow is a *circulating blood volume deficit*, as by hemorrhage, burns, or dehydration, or by regional segregation of blood, e.g., in acute occlusion of portal blood flow, or an acute or *primary insufficiency of cardiac output*, in which there is inadequate blood flow in the tissues. The body compensates immediately by *widespread vasoconstriction*, which varies in intensity in different areas, by the shift of fluid from the extravascular compartments, and by increasing the heart and respiratory rates. In infection, the two above defects may exist (e.g., peritonitis or myocarditis) or the primary disturbance may be *damage of the small blood vessels*.

As shock of any cause continues, the peripheral vascular phenomena which have been observed both clinically and experimentally include vasoconstriction, loss of *vasomotion*, and a swamplike flow in the capillaries and venules. As *venous return declines* progressively, cardiac output follows suit. The effect of deficiency of flow in any given area depends in part upon local compensatory mechanisms. Thus, the brain retains a greater fraction of the available blood flow than the skin and subcutaneous tissues.

The persistence of deficient peripheral flow and the cumulative tissue hypoxia lead to a progressively catabolic state. Metabolic *acidosis* develops. Blood pH and P_{CO_2} decrease, plasma lactate and pyruvate increase, tissue high-energy phosphate is depleted (Rosenbaum et al.). Secretory function declines or disappears. Evidence of *hepatic dysfunction* includes glycogen depletion and late decline in blood sugar, inability to synthesize fibrinogen, prothrombin, and other proteins (Frank, E. D., et al., 1953); increased plasma amino acids (Seligman et al., 1948), evidence of decreased hepatic blood flow (decreased bile secretion, decreased Bromsulfalein clearance). Evidence of *renal insufficiency* includes any or all of the findings of *uremia* (serum potassium elevation may be aggravated by tissue damage). The brain, heart, and adrenal glands still function fairly well unless shock is severe or prolonged.

If recognition of the shock state is too late,

or treatment inadequate, post-mortem examination commonly reveals very little to account for the failure to recover. The causative factor may be evident, but the mechanism of death is frequently obscure. Scattered small hemorrhages in the wall of the intestine are common

EXPERIMENTAL STUDIES

A summary of all the significant work on shock will not be made. The authors propose merely to present an account of the efforts of their laboratory over a period of years (1940–1958) to arrive at a valid concept of the nature of the irreversibility phenomenon Most of the discussion to follow is based upon data derived from a standardized method of producing hemorrhagic shock with predictable consequences. The technique embraces two main principles: (1) that the arterial pressure be maintained at a constant low level, and (2) that the duration of hemorrhagic hypovolemia be determined by physiologic response rather than by arbitrary time limits

Healthy mongrel dogs weighing 18 to 20 kg, fasted 12 hr, given morphine premedication (1 to 2 mg/kg, intramuscularly), and not given barbiturate or general anesthesia, are cannulated under local anesthesia The animal is bled from a femoral artery into an open reservoir elevated at such a height that an arterial pressure of 30 to 40 mm Hg is obtained. Blood clotting in the external system is prevented by the use of small amounts of heparin. Within 30 to 60 min, the blood level in the reservoir reaches a maximum After a variable interval, blood returns to the animal, indicating the failure of compensatory mechanisms. If the blood in the reservoir is reinfused within 2 hr, permanent survival is usually effected (90 per cent) If, on the other hand, the hypotension is allowed to continue, by the fourth hour somewhat less than half the maximum bleeding volume will have returned from the reservoir spontaneously If, at this point, the remainder of the blood in the reservoir is infused intravenously, the arterial pressure will rise toward the initial level and then exhibit a secondary decline. Over 90 per cent of such animals die within 12 hr Post-mortem examination shows no abnormality other than scattered small intestinal hemorrhages and a variable degree of hepatic, renal, splenic, and pulmonary congestion If large volumes of blood or blood substitutes are used in an effort to sustain the circulation, the congestion will be more marked

The condition of these animals is irreversible by blood replacement. They also succumb when treated with additional transfusions (blood substitutes as well as electrolyte solutions), pressor drugs including nor epinephrine, adrenal steroids and ACTH, adrenolytic drugs (except when given prophylactically—see below), and correction of electrolyte disturbances by artificial dialysis Eventually, it seemed likely that the condition under investigation might be a refractory hemodynamic state related to the *functional failure of a critical organ or tissue,* and that after normovolemia had been restored, efforts to stimulate the circulation were beside the point. The brain, heart, lungs, and adrenal glands seemed to be functioning too well to play this role. Renal failure seemed unlikely because of the speed of death. Because of the numerous vital functions of the liver and its special dependence on portal venous blood, which is notoriously low in oxygen content in shock, *the liver* of the animal in shock was perfused by arterial blood, via the portal vein, from a normal donor in balanced cross circulation (Seligman et al., 1947b). *This resulted in a substantial percentage of survivors,* whereas cross circulation via a systemic vein instead of the portal vein was of no value. Was the liver at fault for the loss of a critical function, or because it was the source of a poison generated during sustained anoxia? Most of the dog's tissues in the normal state contain clostridia If they were responsible, *penicillin* should help. When penicillin was administered before the institution of hemorrhage, there was a high percentage of survivors. But pretreatment with polyvalent clostridial antitoxin failed to help. A wide variety of antibiotics was then administered by various routes and at different times before and during shock (Frank, H. et al, 1952c). Pretreatment was found to be necessary to produce survival Even when the antibiotics were administered beginning with the institution of hemorrhage, they were likely to be ineffective. Perhaps most interesting of all was the fact that pretreatment consisting of administration of nonabsorbable antibiotics (*neomycin*) by mouth resulted in survival rates as high as those obtained by any other method, if not higher Although parenteral administration of anti-

biotics was almost as effective as the oral route, the fact that oral neomycin was very effective suggested the importance of the intestinal flora. Moreover, since neomycin does not act against clostridia, these bacteria seemed unimportant

Infection, as it is recognized clinically, was nowhere evident. Blood cultures taken during all phases of shock were uniformly sterile.[1] But many blood and tissue cultures taken just a few minutes after death were positive for a variety of enteric organisms. Thus, the permeability of the intestinal barrier to bacteria or their products came into question as a possible key factor. Nelson reported that botulinus toxin is absorbed from the gut more rapidly in shock than in the normal state. But this is a diffusible toxin and may not reflect the behavior of other types of toxins, e g, endotoxins There is good reason, nevertheless, to assume that bacteria, and perhaps their products, are continuously invading the blood stream during the normal state. This can explain the clostridia in the dog's tissues and other enteric bacteria in tourniqueted muscle. Direct evidence that the gut is permeable to bacteria was obtained by the induction of tourniquet shock in the rat (Friedman et al). This species was chosen because its tissues are uniformly sterile in the normal state. When the muscle of the tourniqueted limb is cultured before release of the tourniquet, it is uniformly sterile, but after removal of the tourniquet, it may exhibit bacteria of intestinal origin If infection from enteric bacteria is responsible, why were they not being cultured during life from the blood and tissues?

Was it possible that the organism in shock is supersensitive to bacteria or their toxins? If so, the few necessary bacteria or their products might be hard to demonstrate. The absence of the signs of infection had already been explained on the basis of the inability of the organism in shock to respond in the usual manner to a bacterial challenge. On the basis of this speculation, experiments were initiated which yielded evidence that there is indeed a markedly lowered resistance to bacteria and their products in shock. This evidence included the demonstration that the phagocytic and bacteriostatic capacity of polymorphonuclear leucocytes and macrophages in shock plasma is reduced[2] (Schweinburg et al, 1955, Rutenburg et al.), that the microscopic appearance of polymorphonuclear leucocytes in shock plasma is abnormal (they simulate "lupus erythematosus cells" with loss of distinct cell membranes, eccentric nuclei, and atypical granules) (Rutenburg *et al.*), *that* the resistance to intravenously injected bacteria of a dog subjected to reversible *hemorrhagic* shock is markedly reduced[3] (Schweinburg et al., 1955), that the *titer of properdin* declines early and severely in hemorrhagic shock[4] (Frank et al, 1955), and that the vulnerability to *endotoxin is* enormously increased (Schweinburg et al., 1954).[5] This last observation *provided quantitative* evidence of a remarkable degree of lowering of resistance to bacterial *products*, even in transient, i e., reversible shock, and confirmed the suspicion that *the amount* of bacterial activity required to produce a lethal effect in shock might be

[1] Time was taken to explore the possibility that

gently to destroy antibacterial potency without altering chemical integrity. Another approach was the study of the effect of antibiotics on the high-energy phosphate content of the liver in shock (Rosenbaum et al.). ...
ing in
nificant

[2] This has been confirmed by the finding that the expected enhancement of the respiratory activity of leucocytes during phagocytosis does not occur in *the presence* of shock plasma (Karnovsky).

[3] These animals succumb to a dose of intra-

[4] This component of *normal serum*, discovered by Pillemer, has been shown to have potent antibacterial activity, especially against gram-negative organisms but *also* against certain gram-positive organisms and viruses

[5] This *experiment* was done in the rabbit because it is possible to assay purified toxins fairly accurately in this species. The toxin used was an *Escherichia coli* endotoxin. The lethal *dose (MLD/100)* of *this toxin* for normal rabbits weighing 5 lb was 0 13 mg The lethal dose (MLD/100) for rabbits previously subjected to less than 2 hr of hemorrhagic hypotension, which alone is uniformly well tolerated, was only 0 00001 mg

so small as to be difficult to detect. On the basis of this finding, it was possible that no more invasion of bacteria or their products than occurs in the normal animal is sufficient to produce fatal peripheral vascular collapse in this very sensitive state.

But all this evidence merely inferred a possible bacterial factor in shock. Confirmation of the presence of a circulating toxin in shock became an essential condition for the validation of the thesis that irreversibility to transfusion is due to a bacterial factor. This was secured during the past year. A search for a poison had been made by many investigators (Moon; Green; Aub, Shorr et al.). The transfer of shock blood to normal recipients does not induce any obvious disturbances. In 1954, however, it had been demonstrated that normal recipients (dogs) tolerated the intraperitoneal injection of homogenated liver from normal or shocked animals, whereas recipients exposed to hemorrhagic shock from which recovery could be expected (transfusion after 2 hr), died if injected with shock liver but recovered if injected with normal liver (Schweinburg et al, 1957). Thus, shock liver contains a substance which is lethal to an animal with lowered resistance. That this was a bacterial substance was demonstrated by prevention of death of the shock recipient by giving him penicillin. A similar technique was applied to test the blood instead of the liver. In both dogs and rabbits, subjected to 2 hr or less of hemorrhagic shock and then transfused with blood from a donor animal in late shock (irreversible), the course in the otherwise reversible recipient is uniformly fatal (Schweinburg et al). These recipients show the characteristic clinical physiologic responses of animals in irreversible hemorrhagic shock and, after death, demonstrate the usual intestinal hemorrhages. Efforts to identify the noxious factor in shock blood have thus far demonstrated that *it resides in the plasma fraction of the blood and that it is a polysaccharide* when extracted according to the Boivin technique (Ravin et al.) It is thus consistent with, but not yet identified as, an endotoxin. Further studies have shown that shock plasma produces the same biologic reactions as intravenously administered endotoxin. Thus in rabbits, there is the characteristic early and remarkable disappearance of circulating polymorphonuclear leucocytes, the typical fever response, the presumably specific generalized Shwartzman reaction (Ravin et al.), and also the induction of tolerance by the "immunizing" administration of either endotoxin or shock plasma (not by normal plasma) against prolonged hemorrhagic hypotension (such animals survive 6 hr of hemorrhagic shock, which is uniformly fatal to unimmunized rabbits) (Smiddy et al.).

Efforts are being made to identify further this lethal factor and to determine the mechanism of its action. Is it a polysaccharide derived not from bacteria but from hypoxic tissues? Landy and Shear have shown that such "tissue toxins" are capable of producing biologic reactions very similar to those of bacterial endotoxins. If endogenous tissue toxins are the lethal factor, it is impossible to answer the question as to how the antibiotics, especially the nonabsorbable intestinal antibiotics, protect against the elaboration of lethal amounts of such tissue toxins during the prolonged anoxia induced by hemorrhagic hypotension. As for the mechanism of action of bacterial endotoxins, there is now much interesting information, which can be summarized briefly by the statement that Reilly, Delaunay, and later Thomas have provided evidence that *these toxins may act via adrenergic pathways* The injection of epinephrine into dogs and rabbits causes disappearance of circulating polymorphonuclear leucocytes, produces fine blood vessel changes similar to those produced by endotoxin, and when injected into the skin following a dose of intravenous endotoxin, produces a markedly enhanced localized necrotizing reaction (Thomas; Zweifach et al, 1956). Furthermore, it has been shown that antiadrenergic drugs, such as *dibenamine*, may be protective in certain forms of shock (Nickerson et al.) and may prevent the lethal outcome when shock blood is transferred to recipients with lowered resistance but protected with dibenamine (Smiddy) But these matters must await future study and experimentation.

The author's present concept of the pathogenesis of shock may be summarized as follows: In shock of any type, generalized tissue anoxia results in marked lowering of resistance to bacteria and their products These products, coming from sites of infection or from the gut

lumen, exert a damaging influence upon the fine blood vessels, possibly via adrenergic pathways, thus aggravating the peripheral vascular insufficiency. The established vicious cycle hastens death (Fig. 14-1).

CLINICAL MANIFESTATIONS

The characteristic features of shock are:

1 *Cold, pale, moist skin*—evidence of the response of the sympathetic nervous system to blood volume deficit or tissue hypoxia There is *widespread vasoconstriction*. Because of the reduced rate of flow in the peripheral vessels, there is *cyanosis* as well as *pallor*, most readily observed in the nail beds and mucous membranes.

2 *Oliguria or anuria*—evidence of reduced renal blood flow

3 *Mental and physical apathy*. Early in shock the patient may be apprehensive and exhibit anxiety owing to release of epinephrine

4. *Hypotension* and *tachycardia*. In many instances, the hypotension is caused directly by reduced blood volume In others, in which there is no deficit (e g , sepsis without significant fluid loss), the *reduced cardiac output* is due to *deficient venous return* owing to stagnation in the periphery because of collapse of the peripheral vascular system.

Infection, a frequent etiologic agent, may be concealed or difficult to detect because of the inability of the organism to respond Therefore, there may be *no* fever, pain, or leucocytosis

LABORATORY DATA

Shock is diagnosed on the basis of bedside evidence Laboratory data are generally not useful for diagnosis but may be helpful in following the treatment.

The measurements which have received greatest attention in clinical shock are those which suggest alterations in blood volume. The *blood hemoglobin* and *hematocrit* are simple and *accurate measurements of the relative* concentration of red cells and plasma in a given sample of blood. They are not measurements of blood volume

Assumptions about blood volume based upon them may be in error for two reasons. The sampled large-vessel hematocrit in shock may be considerably higher than the total blood (body) hematocrit Second, the red cell mass and plasma volume which create the hematocrit may vary independently in either direction In spite of this, the hemoglobin and hematocrit are useful in following the replacement of acute blood losses In *situations in which knowledge* of blood volume is important, the red cell volume and plasma volume must be determined independently [6]

The laboratory findings early in shock depend largely upon the causative trauma.[7] Thus the *hemoglobin and hematocrit may* be high (burn), normal (early hemorrhage, myo-

[6] The techniques used for these determinations must make allowance for prolonged mixing time of the circulating blood in shock.

[7] The examples given in this paragraph are not intended to represent invariable findings but rather to indicate a variety of mechanisms

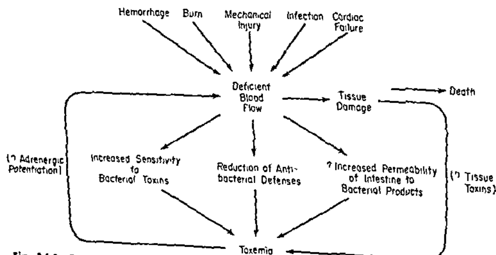


Fig 14-1. Concept of lethal mechanism in shock based upon experimental evidence.

cardial infarction), or low (hemorrhage). The *white blood count* may be high (infection, hemorrhage, myocardial infarction) or low (overwhelming toxemia). The *circulating red cell volume* may be high (polycythemia, epinephrine effect on depots), normal (myocardial infarction, certain infections, early second-degree burns), or low (hemorrhage, certain infections, later burns). The *circulating plasma volume* may be high (myocardial infarction with congestive failure, therapy induced), normal (certain infections), or low (the situation in most shock states).

Measurements of the basic defects in shock of any cause, viz., decreased oxygenation of mixed venous blood and decreased cardiac output, have not been used widely in patients. Simple and safe methods are emerging and will be helpful in solving diagnostic problems and in guiding therapy.

Blood chemistries confirm the failure of hepatic and renal function, indicate the existence of an anaerobic catabolic state, and give evidence of the loss of intracellular components (including certain enzymes [8])

COMPLICATIONS AND PROGNOSIS

The serious complications of shock may be listed in four categories: (1) *Acute hypoxia* of critical areas Sudden fatality during severe insufficiency of peripheral blood flow is usually due to *myocardial infarction* (especially common in the presence of preexisting coronary artery disease) or *brain stem damage* (failure of respiratory or circulatory centers) (2) *Thrombosis of critical vessels.* The lower extremity arteries, the cerebral arteries, or the mesenteric arteries or veins may thrombose (3) *Acute renal insufficiency.* Lower nephron nephrosis may result from either brief and severe or prolonged and moderate depression of renal blood flow. (4) *Shock refractory to therapy.* This may be due to the elaboration of a toxic factor, as suggested by experimental studies

The prognosis of shock depends upon the general condition of the patient prior to shock, the nature and severity of the precipitating cause, the occurrence of serious complications, and the development of irreversibility due to prolonged generalized tissue hypoxia. The clinical impression of unresponsiveness should never deter the physician from continued aggressive therapeutic efforts. More than one patient considered to have an "irreversible" condition is now living and well.

TREATMENT

Every minute saved in the early recognition and treatment of shock is worth hours of last-ditch heroics. Once begun, treatment must be thoroughly effective in order to prevent the progressive and often insidious deterioration which results in unresponsiveness to any and all therapeutic measures. In the presence of profound circulatory collapse, the attending physician must act rapidly [9] to prevent a lethal complication (e g., myocardial infarction, cerebral accident, or lower nephron nephrosis). Emergency resuscitative measures must include *rapid restoration of deficient blood volume* (the magnitude of the deficiency is often underestimated and may approach 50 per cent of the normal volume), *immediate control of continuing hemorrhage,* and the institution of *pressor therapy* if collapse persists in the absence of evidence of hypovolemia. After the vital signs have been restored to reasonable values there is time for a more thorough evaluation of the factors responsible for the deficient peripheral blood flow in the given individual

Is there a persisting deficiency of circulating blood volume? This is often the case and is suggested by the clinical facts (hemorrhage, large burns, extensive tissue trauma, gastrointestinal losses, chronic malnutrition), by direct measurements of red cell and plasma volume, and by therapeutic trial One must learn to

[8] The demonstration of a marked increase in *serum lactic dehydrogenase* and of *transaminase* in experimental shock (Vesell et al.) indicates the need for caution in diagnosing myocardial infarction on the basis of a serum transaminase rise when shock may be responsible.

[9] In this circumstance there is no time to wait for a surgeon, for elaborate instrument kits, or even for sterile instruments, unless these are immediately available. Remember that the brain cannot tolerate severe anoxia for more than a minute or two. If a superficial vein is not easily found for venipuncture (try the external jugular vein, which will usually fill if compressed above the clavicle), expose an upper extremity vein and insert a large cannula or plastic tube for administration of whole blood, blood fractions, or pressor drugs as indicated Type "O," Rh-negative blood is useful while awaiting cross matching.

treat the patient and not the laboratory data (Moore). The patient in congestive heart failure or in certain types of septic shock (e.g., peritonitis) may not tolerate the rapid restoration of a "normal" blood volume, hematocrit, serum sodium concentration, etc. *Pulmonary edema* may intervene. One should be guided by the pulse, respiration (including frequent pulmonary auscultation for early evidence of edema), arterial pressure, sensorium, skin temperature, and urine flow (an in-dwelling catheter for hourly output observations is often indicated). *If urine formation is insufficient (less than about 0.5 ml/min), this indicates persisting shock* (decreased renal blood flow) unless there is preexisting or concurrent renal damage. The latter possibility may be tested, without risk of seriously overloading the circulation, by the rapid infusion of 500 ml of 5 per cent glucose in water. A transient rise in the rate of urine formation will demonstrate persisting blood volume deficiency. No rise will suggest renal damage and the need to avoid overhydration.

The pressor drug *norepinephrine* (noradrenaline, levarterenol) may be lifesaving if shock persists in the face of a relatively normal blood volume. If the blood volume is deficient, a normal arterial pressure induced by pressor drugs may offer false security in the presence of a persisting inadequacy of peripheral blood flow. In experimental normovolemic shock, the drug effects a marked increase in cerebral, coronary,[10] and adrenal blood flow rate. The hepatic flow is unchanged. The renal blood flow is decreased. Cardiac output may or may not be increased. Norepinephrine should be administered as a constant intravenous drip in relatively low concentrations (4 to 8 ml *Levophed*[11] per liter) and via an inlying plastic tube. This will minimize the possibility of extravascular infiltration, which causes serious necrosis of skin and subcutaneous tissues. The infusion rate should be adjusted so as to maintain a reasonable arterial pressure. If increasing amounts of the drug are required, the physician should try to stabilize at a lower arterial pressure, which will be acceptable if the patient is alert, comfortable, and forming urine.[12] If this is not possible, persisting hypovolemia or untreated infection should be suspected. When the drug is no longer needed, the infusion should be terminated gradually in order to avoid significant hypotension.

There are two major facts about *infection in shock:* (1) in the presence of uncontrolled infection, even though apparently mild, *no treatment overlooking the infection is likely to succeed;* (2) sepsis may be difficult or impossible to recognize once shock has supervened. This is because the usual clinical evidences (fever, leucocytosis, pain) may be *completely masked by shock.*[13] Furthermore, shock may be the initial and only evidence of major infection. Therefore, a high index of suspicion is essential. Chests, abdomens, wounds, blood, urine, sputum, and other possibly infected areas must be investigated and appropriate surgery and antibiotics introduced early. Experimental evidence suggests the desirability of administering nonabsorbable intestinal antibiotics to all patients in shock to minimize the absorption of bacterial products from the intestinal lumen. The experimental value of the antiadrenergic drug, *dibenamine,* in the prevention of death due to transient occlusion of the arterial blood supply of the intestine (Shapiro et al.) suggests the need for clinical evaluation of this drug in clinical shock and in intestinal infarction.

Sedatives and narcotics must be used skillfully, if at all, to relieve pain and apprehension. There are increased sensitivity to and decreased elimination of these drugs in shock. They may aggravate shock by decreasing cardiac output. Small test doses are advisable. The necessary medication is best given intravenously to avoid the possibility of faulty absorption from ischemic tissues.

It is no longer considered advisable to apply extra blankets to warm the cold skin of the patient in shock. This may aggravate the shock state by countering surface vasoconstriction and enlarging the total vascular bed, thus diminishing available blood flow to more critical

[10] Isolated bovine coronary arteries dilate in response to this drug (Oppelt).

[11] Trade name for norepinephrine by Winthrop Laboratories, New York, N.Y.

[12] Noren [illegible] by de- [illegible] ct must

[illegible] cases of fatal [illegible] which at autopsy proved to be due to unsuspected peritonitis.

areas. The value of body cooling on the other hand remains to be more thoroughly studied.

If shock is unresponsive to volume replacement, pressor therapy, and treatment of infection, the use of *adrenal cortical steroids* should be considered. A clinical course of prolonged or severe physical strain, an electrolyte disturbance consistent with cortical insufficiency, an eosinophil count which is not severely depressed may favor this decision. Individual case reports suggest the value of such therapy even in the presence of obvious sepsis (Ebert) and even though experimental and recent clinical studies do not demonstrate cortical insufficiency in shock (Frank, H. A., et al., 1955a; Kass).

Glucose (at least 150 Gm/day) should be administered intravenously, in continuous or divided doses to prevent hypoglycemia and spare body proteins Water-soluble vitamins (B and C) should be given in large doses

Special Aspects of Cardiogenic Shock. The commonest shock-producing event of cardiac origin is *myocardial infarction* When shock accompanies this disorder, the prognosis is ominous. If the infarction is "silent," early diagnosis may be difficult and important because excessive blood or fluid therapy may easily provoke pulmonary edema In the absence of congestive failure, the *central venous pressure is thought to be low, as in other forms of shock* (Gootnick et al) The blood volume is apt to be close to normal, although slightly decreased plasma volume and slight hemoconcentration have been reported (Stead et al) If the infarction is secondary to blood loss, replacement transfusions are clearly indicated to improve coronary and general peripheral flow The value of transfusions during normovolemic cardiogenic shock is not so certain, although there may be some benefit from slow, small transfusions (Epstein et al.). It may be advantageous to administer *red cells*, instead of whole blood, to minimize the production of pulmonary edema while providing increased oxygen transport and possibly also an increased plasma volume at the expense of extravascular fluid (Moore et al). The use of arterial instead of venous transfusions has been advised by some (Page) to effect an increased arterial pressure and increased coronary flow before the increased cardiac work load must be met The clinical advantage of this approach is not established but seems questionable.[14]

If shock and pulmonary edema coexist, the physician is often in the difficult position of accepting the former or aggravating the latter The choice must always be made in favor of the treatment of the shock, however, because failure to do so is uniformly fatal. Here the physician must be in constant attendance to evaluate the severity of pulmonary edema, the sensorium, the urine flow, and the need for narcotics and sedatives, cardiac drugs, transfusions, limb tourniquets, pressor drugs, etc., in a situation of rapidly changing responses (For treatment of Pulmonary Edema associated with shock, see Part 18, Chap. 14.)

In recent years, there has been general agreement as to the great value of *norepinephrine* in the treatment of shock secondary to myocardial infarction. The experimental demonstration of a manifold increase in coronary and cerebral blood flow in response to this drug is confirmatory (Frank, E. D., et al, 1956) Fortunately, the negative effect of this agent upon renal blood flow and urine formation in the dog is not seen commonly in man, nevertheless it must be watched for (Moyer et al.). Necessary precautions in the use of norepinephrine are described above.

The value of a *high oxygen content* in the inspired air needs no comment but is secondary in importance to the restoration of peripheral blood flow. The use of drugs to improve cardiac function is described elsewhere (Part 19). One must be mindful of the danger of digitalis intoxication during potassium diuresis in successfully treated shock

In the over-all management of cardiac disease, two therapy-induced shock states deserve brief comment One is *the use of acidifying diuretics (e g , ammonium chloride)* in the presence of renal insufficiency (inability to form an acid urine) This may precipitate acute acidosis, oliguria, acute respiratory distress, and circulatory collapse. The other shock state results from *severe, chronic restriction of sodium* in the diet (under 200 mg daily). This may produce the *low-salt syndrome* (anorexia,

[14] Projected clinical research includes efforts to bypass the heart and the lungs during cardiogenic shock by using extracorporeal pumps and oxygenators

vomiting, weakness), adrenal cortical exhaustion, vitamin B depletion (low protein intake), oliguria, and circulatory collapse.

A detailed description of the treatment of shock-induced lower nephron nephrosis is beyond the scope of this chapter. Management is based upon avoidance of overhydration, provision of calories (5 to 25 per cent glucose intravenously) to minimize protein catabolism, and careful observation for serious sequelae (potassium intoxication, acidosis, tetany, pulmonary edema, central nervous system irritability followed by depression) which may indicate the need for peritoneal irrigation or kidney dialysis through the use of the so-called "artificial kidney."

METABOLIC ASPECTS OF SHOCK

The term "shock" has been used to embrace a number of seemingly similar states induced by a wide variety of agents and conditions. It cannot be defined in precise terms. A precarious state of the circulation is a central factor; there is insufficient blood flow and return, resulting in variable and inadequate nourishment (in its broadest sense) of organs and tissues. This impairment is characteristically correctable in an early stage but later becomes "irreversible," *i.e.*, refractory to current therapeutic measures. The specific physiologic and metabolic disturbances which may determine "irreversibility" (and thus death from shock despite treatment) are not yet known.

Much of the information regarding the metabolism of shock has been obtained from animal experimentation, the shock having been produced by various methods and under diverse conditions. Many of the controversial and often contradictory findings may be reconciled through consideration of these variables.

The shock syndrome is the result of a noxious stimulus, the direct effects of this stimulus, and, most importantly, the reactions of the organism to it. The nature, extent, and persistence of these reactions depend upon (1) the preshock physiologic status of the organism, (2) the nature, intensity, and duration of the noxious stimulus, and (3) the promptness of the removal of the stimulus. The correction of the immediate damaging effects of the stimulus and the rapid application of the best available local and systemic resuscitative measures are clearly important.

Ingle (1951) has emphasized that species, heredity, sex, age, nutritional status, diet, previous exposure, emotionality, activity, and bacterial pattern are some of "the extrinsic and intrinsic variables which affect the nature and extent of metabolic adjustment." He has called these variables ". . . 'heteropoietic' for, when they change in value, they tend to cause differences in metabolic responses."

In addition to the problem of *heteropoietic variables*, one must take into account the shock-inducing procedures themselves, and the assortment of arbitrary criteria used for recognizing the existence of shock. These procedures and criteria determine, to a large extent, which metabolic alterations will occur at a particular "stage" of shock, and which metabolic alterations the experimenter will recognize as signs of a fatal or favorable eventual outcome.

Hypoxia is a common feature of shock, irrespective of the type of initiating stimulus; inadequate circulation is its basic cause, curtailment of oxygen and nutrient delivery are its main features. In addition, as a result of *diminished* venous blood flow and probable diminished lymphatic flow (except from areas directly traumatized), there is an "*accumulation*" of various metabolites. These may affect the local tissue circulation and metabolism and also, by being carried elsewhere, the metabolism and circulation of other areas. Profound metabolic changes result. Effects of *hypoxia* manifest themselves earlier in some tissues than in others. *The sequence is probably due to varying susceptibility of different tissues to oxygen deficiency*, to the pattern of *compensatory circulatory adjustment*, and to *redistribution of blood flow*. In addition, a developing inability of tissues to use oxygen would further contribute to metabolic abnormalities. The vascular compensatory activities compromise particularly the circulation to the kidneys and certain *splanchnic* viscera. The requirements for immediate survival of the organism are met by sacrifice of function of some of its parts;

once the crisis is over, however, impairment of organ function may be permanent and result in death.

A general pattern of metabolic changes seems to be characteristic of, but not necessarily specific for, the shock syndrome. It involves proteins, carbohydrates, fats, water, vitamins, endocrines, and electrolytes; the response is dynamic, with an ever-changing but generally predictable pattern.

The *early metabolic responses of shock* are generally indistinguishable from the pattern of reactions that results from other stresses, some of these early biochemical alterations may be spontaneously reversible if the injury is not severe, or may be readily corrected by prompt and suitable therapy. The biochemical alterations that occur as shock progresses have, for the most part, not been identified as anything other than the results of the hypoxia that accompanies persistent deficiency in blood flow. Furthermore, none of these alterations has as yet been unequivocably linked to the lethality of shock.

Some of the usual features of the metabolic changes in shock are decreased oxygen consumption and body temperature, hyperglycemia, lactacidemia, pyruvicacidemia, impaired glucose tolerance, acidosis, increased breakdown of certain tissue proteins, *azotemia*, retention of sodium, chloride, and water, and an abrupt drop in blood ascorbic acid. These changes are usually accompanied by involution of lymphoid tissue and thymus, lymphopenia and eosinopenia, leucocytosis, increased pituitary-adrenal activity with associated depletion of adrenocortical cholesterol and ascorbic acid, and an increase in some blood adrenal hormones, both medullary and cortical The concentration of antidiuretic hormone in the blood is also greater. Liver function is impaired, as evidenced by an increase in Bromsulfalein retention, a decrease in the rate of conjugation of certain adrenal steroids, a decreased ability of the liver to synthesize glycogen, to deaminate certain amino acids, and to build urea.

All metabolites are interrelated, and in the final analysis, all must be considered together The forthcoming separate characterization of the behavior of the metabolites in shock is arbitrary and has been adopted only in order to facilitate exposition.

WATER AND ELECTROLYTES

A clear distinction must be made between the effect of the injury and that of shock. Sudden serious disturbances of water, electrolytes, and plasma proteins may result directly from the initial injury, independently of and not as a consequence of shock, in fact, these changes may be the primary initiators of certain forms of shock, e.g., burn. It has been known for a long time that the early movement of blood constituents into, adjacent to, and from the injured area may lead to fatal depletion of water, electrolytes, and protein, if adequate replacement therapy is provided, death may be averted. After injury, blood volume is generally low, interstitial space is variable, depending primarily on the nature and extent of the blood plasma and fluid losses. Plasma sodium and chloride concentrations may be normal or low, while plasma potassium is normal or slightly high. There is a shift of sodium into injured cells, with a concomitant outward flow of potassium and hydrogen ion Sodium and chloride excretions are initially low, that of potassium is high These changes in urinary electrolyte excretion seem to reflect primarily the changes in fluid and electrolyte distribution in the injured animal, there may be also direct hormonal influences on the kidney, such as may result from increased adrenal cortical activity (aldosterone?) and increased antidiuretic hormone activity. If shock supervenes, *urine output slows or stops*, and sweating, vomiting, abdominal distention, and diarrhea may occur, sodium enters cells and potassium leaves, resulting in hyponatremia and hyperpotassemia These electrolyte shifts occur not only in injured areas, but also generally and may result from the tissue hypoxia of shock Plasma potassium may also rise as a result of cellular release of potassium associated with the net breakdown of tissue protein and glycogen The untreated shocked animal becomes increasingly sensitive to extracellular potassium, even though the hyperpotassemia is usually quantitatively small during shock; however, concentrations sufficient to cause death are frequently encountered near death. The toxic effects of potassium may be accentuated by hyponatremia or hypocalcemia Plasma magnesium concentration may rise in peripheral circulatory failure

In shock, *blood volume is decreased*, since the fluid influx into injured areas comes mainly from the blood. *In the absence of hemorrhage*, this decrease is principally *of the plasma*, but there are also fluid and electrolyte shifts from uninjured areas resulting in their *dehydration*. The specific quantitative electrolyte and fluid changes of the various organs and tissues are incompletely known

There is a slackening of transcapillary water movement as measured by D_2O [the symbol for "heavy water" (deuterium oxide)], this is interpreted as due primarily to a decrease in functional capillary area Present evidence indicates that there is no generalized increase in capillary permeability in shock; only the capillaries in the injured area definitely "leak," though *in some species*, late in severe shock, the capillaries of the intestinal tract and heart are congested, bleed, and may be abnormally permeable There is no clear evidence to suggest that these changes stem from alterations in endocrine function.

(Rosenthal, S M, et al)

PROTEINS

Present evidence best supports the idea of a dynamic interchange of most body constituents Borsook and Keighley are generally considered the originators of this concept; Schoenheimer, Whipple, their coworkers, and others developed the picture of *a dynamic steady state among body proteins* in adults This thesis rests on the existence of three possible continuing processes. (1) proteins are completely degraded into amino acids, which are then resynthesized into new proteins, (2) proteins could be partially degraded to peptides, which would then be reassembled into different proteins, and (3) synthesis of certain proteins could occur by transformation of existing proteins Only the existence of the first process has firm support to date.

Schoenheimer, Rittenberg, and associates demonstrated with labeled amino acids that the structures of most proteins are not fixed, but that their constituent amino acids are undergoing interchanges with the free amino acids of their environment. The *rate of* interchange varies with the protein involved In order to maintain this apparent steady state, there must be a very precise balance between protein synthesis and degradation.

This steady state is altered during shock so that there is an increased breakdown of body protein. The specific mechanisms underlying this change have not been fully defined—some are local and perhaps unique to areas directly damaged by the initiating trauma; others are general and seemingly similar for a wide variety of injuries. While the over-all systemic metabolic reaction to injury results in a net increase of total tissue catabolism over total tissue anabolism, each tissue presumably metabolizes in its own fashion, and there may be strikingly different net anabolic and catabolic rates among various tissues in shock (Cuthbertson). Unfortunately, the pattern consequent to shock is incompletely known.

Plasma protein concentrations may change in shock (particularly in shock caused by traumas and burns), not only because of the shifts and losses of water and electrolytes already described, but also because of shifts and losses of the plasma proteins themselves Plasma protein may be lost directly from the site of injury (e g, from superficially burned areas) or by hemorrhage, or it may be temporarily sequestered in injured areas. As shock progresses, plasma protein which at first had entered and left the injured areas rapidly, now exchanges *more slowly*, and its reentry into the lymph or blood is delayed In untreated hemorrhagic shock, *mild hypoproteinemia* develops as a result of the plasma loss and its partial replacement by protein-poor extravascular fluid, the decreases of albumin and globulin are proportionate In contrast, plasma albumin drops disproportionately in severely burned or wounded subjects, this results from the faster passage of albumin through the directly damaged capillaries.

Plasma prothrombin and fibrinogen fall in severe shock; there is usually an accompanying increase in fibrinolytic and other proteolytic activities Properdin may decrease abruptly, the significance of this is not established.

Rises in plasma nonprotein nitrogen are almost constant accompaniments of severe shock; the over-all increased tissue protein breakdown and the oliguria characteristic of shock combine to lead to the elevated concentrations of most of the plasma nonprotein nitrogen (NPN) components, e g, urea, creatinine, uric acid, and amino nitrogen Generally, these increases are proportional to the severity of the initial

injury and the severity of the succeeding shock state.

The behavior of *amino acids* in shock has received special attention during recent years, because of the central role of the amino acids in the metabolism of proteins and in the interrelationships among proteins, carbohydrates, and fats.

Postulates of amino acid "pools" have been put on an experimental basis by the use of isotope experiments, and studies by Campbell et al., Miller et al., and Borsook et al. have shown that in rats, rabbits, and mice, plasma amino acids have an extremely rapid turnover rate—of the order of minutes. The plasma amino acid levels might be subject to at least the following influences: food intake, intestinal absorption, transcapillary and transcellular exchange, deamination, transamination, decarboxylation, interchange among amino acids, protein, carbohydrates, and fats, and renal excretion and reabsorption

The plasma amino acids in normal individuals are relatively unchanged from day to day except for the effects of diet Any wide fluctuations unrelated to feeding assume great significance—they indicate, probably, a basic upset in the body economy.

Increases in the plasma concentration of the total free amino nitrogen are characteristically observed in severe shock (Sayers, M A, et al., Engel et al, 1943). This increase may begin early and then rise progressively as shock becomes more profound and prolonged Indeed, Sayers and associates found that an early rise in plasma amino nitrogen during the initial 1 hr of bleeding used by them to initiate hemorrhagic shock in rats meant death for these animals if untreated, while similarly bled and untreated rats without the early rise in amino nitrogen lived. However, even marked rises in plasma amino nitrogen had no adverse prognostic significance if appropriate transfusion therapy was given

Though *renal dysfunction* is a constant accompaniment of severe shock, it can play only a secondary role in aminoacidemia (Rosen et al., 1958).

The rate and degree of plasma amino nitrogen elevation vary with the type of shock. They are greater if direct tissue damage is present (tourniquet, crush, burns). There is evidence that amino compounds are "produced" in disproportionately large amounts in the injured areas and, in these types of shock, account for the earliest increases which may precede the onset of hypotension. Later, as other organs become "damaged" as a result of the reduced circulation, there is a more generalized tissue contribution of plasma amino compounds. The increased release of amino acids from certain peripheral tissues (e g, muscle) of the shocked animal presumably reflects an increased protein breakdown to protein synthesis ratio, a change in the normal steady state. Late in severe shock not only do amino compounds enter the plasma in increased amounts, but their "removal" from the plasma by the liver may be slowed Liver slices from rats in hemorrhagic shock deaminate amino acids and form urea slowly; similarly, the ability of liver slices from burned rats to deaminate alanine is impaired This may be because of *hepatic hypoxia* (Engel et al., 1944); arrest of the circulation to the liver of rats in vivo leads to progressive failure of the liver to remove amino acids from the blood. Shocked dogs, though, retain the ability to clear certain amino acids injected intravenously in large amounts; Seligman and associates (1948) interpret this to mean that the amino acidemia of shock represents *deficient blood flow to the liver* rather than specific impairment of liver function per se.

Unfortunately, most of the information regarding plasma amino compounds in shock derives from studies in which only total amino nitrogen concentration has been measured by one or more colorimetric methods not wholly specific for amino acids In a few investigations, the more specific gasometric ninhydrin method has been used, but it also yields information only about the behavior of the twenty-odd amino acids lumped together When 19 amino compounds were measured individually by an ion exchange chromatographic technique in ultrafiltrates of plasma and serum from normal and untreated severely burned rats (80 per cent mortality in 12 hr), the free amino nitrogen rise was not proportionate among the individual amino compounds In fact, about three-quarters of the rise was accounted for by an increase in taurine and a newly found amino conjugate fraction (Rosen et al, 1953) Asparagine, isoleucine, leucine, tyrosine, phenylalanine, and histidine were also increased, while proline and valine were decreased The amino conjugate fraction rose fourfold (proportionate to the plasma NPN and urea), its composition was similar in the normal

and unburned rats—glutamic acid and glycine were predominant; alanine, proline, serine, threonine, valine, and leucine were present in lesser amounts

Very little information is available in man, and that available is difficult to interpret, since the patients studied had undergone many severe stresses which might influence plasma amino acid levels. These stresses included the initial severe wounding (complicated and variable), hemorrhage, shock, anesthesia, operation, fluid and electrolyte imbalance, fever, infection, antibiotics, and intravenous infusions (blood, albumin, gelatin, etc.). During shock, as in the case of rats, no general increase in the plasma amino acids of these patients occurred—alanine, in particular, phenylalanine, tyrosine, lysine, and taurine were usually increased; isoleucine, proline, and glycine were decreased (Levenson et al). In patients with severe liver disease, but not shock, methionine, tyrosine, and phenylalanine are most commonly elevated.

Various hormones affect amino acid metabolism and, thereby, the levels of the plasma amino acids. Noall and coworkers, using a nonmetabolizable amino acid as a "tracer," have recently presented evidence suggesting that many hormones modify the rate of transport of amino acids across cell membranes But what roles the various hormones play in the changes of plasma amino acids in shock is not known Increase in plasma amino nitrogen follows administration of large doses of certain adrenal hormones, but an intact pituitary-adrenal system is not essential for the aminoacidemia seen in burned rats. Although injection of insulin will lower the concentration of amino nitrogen in the plasma, the amount of insulin required is enough to produce signs and symptoms of hypoglycemia

Elevations in blood ammonia concentration are commonly observed late in shock, but so far as is known, significant toxicity therefrom almost never occurs, except in patients with serious liver disorders and severe gastrointestinal bleeding. The rise in ammonia stems, in part, from a decreased ability of the liver (rat) to form urea (Engel et al , 1946)

CARBOHYDRATES

Claude Bernard (1877) is credited with being the first to indicate that hemorrhage produces hyperglycemia. This observation has subsequently been confirmed in various species and with different shock-inducing procedures, illnesses, and injuries.

Neuroendocrine mechanisms which mobilize the cellular stores of carbohydrate are activated by trauma, giving rise to *a prompt increase of blood glucose before shock is evident. Hyperglycemia* usually persists into advanced shock until the terminal stages, when blood glucose may fall to subnormal levels, especially when environmental temperature is high (Trusler et al.).

In hemorrhagic shock, hyperglycemia is accompanied by *an increase in blood lactate and pyruvate levels,* which continue to rise concomitantly with liver and muscle glycogen depletion as shock progresses (Haist, 1946). The metabolism of glucose by the peripheral tissues may be greatly increased early. There is ultimately a proportionately greater increase in lactic acid, resulting in an elevated lactate/pyruvate ratio which may reflect a predominance of anaerobic over aerobic carbohydrate metabolism, intravascular glycolysis as a consequence of prolonged hypoxemia has also been held accountable for this change.

Preinjury liver glycogen depletion, adrenal demedullation, adrenalectomy, evisceration (hepatectomy), or occlusion of the afferent and efferent blood flow of the liver not only prevent the postinjury rise in blood glucose but usually result in hypoglycemia Although the processes of carbohydrate mobilization are highly complex and incompletely known or understood, it is generally agreed that hepatic glycogenolysis, presumably by epinephrine that is reflexly released, is chiefly responsible for the early hyperglycemia Other evidence suggests that, in addition, nervous stimuli and blood-flow alterations may act directly on the liver and thereby influence glycogen breakdown. Glucocorticoids inhibit peripheral utilization of glucose and promote gluconeogenesis and glycogenesis However, the hyperglycemic response occurs after trauma of the adrenalectomized animal that is maintained on saline solution and DOCA and fed, or instead, fasted and given a fixed dose of corticoid that alone does not alter the blood glucose level (Engel *et al*, 1937) (See page 14-32 for further discussion of interpretation of this sort of experiment) New formation of carbohydrate from lactate, pyruvate, and possibly amino acids deriving from peripheral tissues helps maintain the hyperglycemia as the glycogen stores are be-

ing depleted; this is likely, since a sustained hyperglycemia occurs in the prefasted but otherwise normal rat after hemorrhage. There is the further possibility that under certain conditions the peripheral utilization of glucose may be inhibited by both corticoids and epinephrine.

The *hypoglycemia* that develops later in shock is generally considered a result of a depletion of liver and muscle glycogen, the absence or reduction of gluconeogenesis and glycogen formation and the often-mentioned increased glucose metabolism by the peripheral tissues underlie these depletions. The importance of this last factor is demonstrated by the finding that hemorrhage results in a very rapid fall of blood sugar in adrenodemedullated eviscerated rats.

Dogs in late oligemic shock have elevated blood levels of pyruvate and lactate with an increase in the lactate/pyruvate ratio. Reinfusion of the shed blood is followed by a prompt return of these constituents to normal levels whether or not animals subsequently die. Blood-clearance studies of lactate, pyruvate, or glucose injected during hemorrhagic hypotension (Lamson bottle technique) indicate that these dogs clear the blood lactate essentially as well as nonhemorrhaged dogs, but the clearance of pyruvate is somewhat below normal and that of glucose is markedly reduced. When the blood is returned, the blood clearances of glucose and pyruvate return to normal. These observations may signify that the piling up of these metabolites during hemorrhagic shock may result from poor blood flow and that a critical hepatic enzymatic derangement is not involved (Seligman et al., 1947). However, some experiments with rats suggest that impairment in liver function does occur late in hemorrhagic shock. The evidence of how glucose is utilized by the peripheral tissues in shock is still controversial.

As already mentioned, the precise role of the *adrenal hormones* and their intimate interrelationship with other hormones after injury and shock are unknown. After hemorrhage, adrenalectomized dogs have an elevation of blood lactate and pyruvate, as do intact animals, but the blood glucose level falls, unlike the response of normal dogs, blood lactate and pyruvate remain elevated after transfusion, possibly because of the absence of corticoids and the gluconeogenesis which they support. Continuous intravenous infusion of epinephrine into normal dogs results in changes of blood lactic and pyruvic acids that are not so marked as those occurring after hemorrhagic shock. These observations suggest that the alterations of blood lactic and pyruvic acids in hemorrhagic shock are not solely attributable to epinephrine or corticosteroids, and are not necessarily correlated with the blood glucose level. The possible participation of *glucagon* (the pancreatic hyperglycemic factor) in the glycemic response has not been evaluated, nor is there presently any quantitative information on the sequential alterations of growth hormone activity during shock.

During the induction of *limb ischemia*, i.e., while the occlusive device is in place, there is a rise in blood sugar, lactate, and pyruvate which is ascribed to *sympathetic stimulation* from the pressure of occlusion; following tourniquet release and the development of shock, a marked further increase in these blood constituents and an increase in the lactate/pyruvate ratio occurs (Haist et al., 1944). The sudden increase in lactate is, in part, attributable to its release from the hypoxic limbs. The hyperglycemia after tourniquet release is ascribed to the liberation of epinephrine. As shock progresses, the hyperglycemia is sustained, while, for the most part, the lactate/pyruvate ratio does not deviate markedly from normal. Terminally, blood lactate accumulates again as the blood sugar falls to subnormal levels.

Tourniquet shock results in a reduction of the glycogen stores of the liver and the muscles of the uninjured as well as the injured extremities, depletion of glycogen with shock occurs whether or not the animals have been fasted, and is greater than that found in fasted normal animals or in animals with the tourniquets in place. Tourniquet-shock animals have a reduced tolerance for administered glucose, which correlates with the duration of limb ischemia and their inability to store glycogen in liver and muscle even on insulin administration, which, however, lowers the blood sugar. The later fall of blood glucose in the shocked animals, below that of control animals, while the liver and muscle stores of glycogen are being depleted suggests that carbohydrate is not being formed from noncarbohydrate sources or that greater amounts of sugar are being metabolized peripherally, or that both these factors are involved. Since exogenous insulin reduces blood sugar in the shocked animal, the presence of hyperglycemia suggests that during shock, either the blood sugar level is not regulating endogenous insulin secretion, or normal insulin activity may be deranged or blocked.

(Stoner et al., 1952a.)

FATS

Little is known of fat metabolism in shock Engel and Hewson found that the fasting ketosis of rats anesthetized with Nembutal is promptly suppressed by mild hemorrhage Severe hemorrhagic shock (associated with a rise in plasma amino nitrogen concentration) results in a progressive hypoketonemia and an inhibition of a rise in blood ketones following infusions of sodium octanoate These same changes were noted in adrenalectomized rats (maintained on DOCA and saline solution) subjected to hemorrhagic hypotension and shock Engel and Hewsin point out that these findings may be due to either a depressed hepatic production of ketone bodies or an accelerated utilization by the peripheral tissues, or both The hepatic production of ketones may be depressed because of impaired delivery of ketone precursors to the liver secondary to reduced hepatic blood flow or to impaired oxidation of fatty acids by the liver.

Adrenal cortical lipids (total and cholesterol) decrease rapidly in domesticated rats subjected to hemorrhage, tourniquet, burn, and traumatic shock Coincidentally, there is a drop in adrenal ascorbic acid In many feral species, these changes do not occur, nor do they in domesticated rats adapted, by repeated exposures, to the stressor (Woods). Increases in certain serum lipoproteins, cholesterol, and lipid phosphorus follow many types of injuries in which tissues are directly damaged–but these changes are not consequent to shock

NEUROENDOCRINE FACTORS

Some evidence has already been cited that certain of the metabolic reactions to injury and shock may be mediated through the neuroendocrine system Early impetus for this view came from the observations and writings of Claude Bernard, Cannon, and Selye The state of adrenal function was noted to influence profoundly the capacity of the organism to respond to injury An abrupt increase in adrenal medullary activity following injury was demonstrated early Later, Selye reported tissue disintegration, cellular atrophy, and even necrosis in various tissues, with the notable exception of the adrenal cortex, which, on the contrary, almost invariably hypertrophied. *These changes in the adrenal glands have since been correlated with an early increased secretion of certain adrenal hormones, medullary and cortical (e.g., aldosterone, hydrocortisone, epinephrine, and norepinephrine)*. Many manifestations of the usual reactions to injury were not found in adrenalectomized animals. It was further noted that the resistance of adrenalectomized animals to exogenous stressors is low; this confirmed what clinicians had long known about patients with Addison's disease.

A relationship between the pituitary and adrenal glands in these physiologic responses was demonstrated in the early studies. It was known that adrenal cortical atrophy occurred following hypophysectomy and that hypophysectomy, like adrenalectomy, prevents the usual reactions to stressing stimuli. Extension of these observations led Selye to formulate his concept of the *general adaptation syndrome*. Later observations showed that ablation or stimulation of certain areas of the hypothalamus either depress or activate the secretion of ACTH There has been much discussion about how the hypothalamic-pituitary-adrenal system is activated, nervous, metabolic, and circulatory factors are involved (see Part 2, Chap 30).

After injury, certain hormones are apparently secreted in amounts capable of causing metabolic upsets when given in situations of no stress. Further, many of the biochemical responses to injury seem to be related to the presence of an injury of a certain severity rather than to one of a specific type, and in this sense, seem nonspecific Since many of these metabolic changes are similar to those induced by administration of certain pituitary and adrenal hormones, increase in central nervous system, hypothalamic, pituitary, and adrenal activity has been considered important in the development of the metabolic reaction to injury This thesis has gained some support from the findings that (1) many of these changes do not occur in the unsupported adrenalectomized animal, and (2) some of the metabolic changes and the apparently increased adrenal hormone secretion roughly parallel the severity of the injury

The precise manner in which hormones modify metabolic reactions is not known. It seems clear that they do not initiate new reactions.

Biochemical studies of cell fractions have revealed that metabolic sequences are more or less restricted to certain discrete structural units within

the cell; i.e., the ultrastructural and spatial organization may be of importance in the regulation of metabolic processes in the cell. This is particularly evident when the tissue slice or intact mitochondria is required to observe certain reactions. It is believed that the hormones may primarily influence cellular metabolism at this "enzyme-structure level" ("cytoskeleton" of Peters) instead of at the "enzyme level," the classical, more "primitive" method of control in which the vitamins, antimetabolites, and enzyme inhibitors apparently exert their influence on metabolism, and the level at which substrate and enzyme competition and the pure "biochemical lesion" are operative (Rossiter).

Cori stated that "although phosphorylase has been implicated in the metabolic action of epinephrine, hexokinase in that of insulin, and oxidative phosphorylation in that of thyroxine, none of these systems is sufficiently well understood to make one confident that the results obtained so far explain the actions of these hormones."

It is generally accepted that there is an association between the extent of metabolic response to injury and shock and the level of adrenal hormones secreted. The level of adrenal hormones necessary in adrenalectomized animals for the full metabolic reaction depends on the severity of the injury.

"The adrenal cortical steroids and the epinephrines appear to operate largely as a functional unit physiologically. The multiple sites of action and character of tissue and organ responses to the two species of hormones are strikingly similar Many actions attributed to the steroids may be ascribed, in effect, to action of the epinephrines Many actions of the epinephrines are not elicited in the absence of steroids. Corticoids and neurohumors are not interchangeable, however Steroids maintain the integrity and responsiveness of tissues in the process of reacting to the epinephrines This relationship is best seen on exposure to stress, when the defect of steroid lack may be elicited by heightened sympathetic-medullary activity In the absence of the corticoids, responses to the neurohumors are progressively lost, while the destructive symptoms of adrenal insufficiency are progressively exhibited" (Ramey and Goldstein).

Certain studies have demonstrated the occurrence of some of the biochemical changes associated with injury in the presumed absence of any concomitant increase in adrenal hormone production.

Ingle et al. and Toby and Noble found the same increase in urinary nitrogen excretion following fractures in adrenalectomized rats on maintenance adrenal cortical extract and in sham-operated controls, no increase was found in adrenalectomized rats maintained on saline solution. Similar observations of the occurrence of hyperglycemia in traumatic shock (Selye et al, 1941) have been made

Ingle concluded that the negative nitrogen balance resulting from injury requires the presence of adrenocortical hormones but is not specifically caused by an increase in their secretion. Ingle calls this the "permissive" or "supporting" action of the adrenocortical hormones, and Selye, from a different point of view, speaks of the "conditioning" action of these hormones. Certain responses to the adrenal steroids are modified by associated systemic stress. This may result from a decrease in "inactivation" of circulating steroids by the liver or a change in target-tissue reactivity. Further, the possibility exists that in adrenalectomized animals kept on maintenance doses of adrenal hormones, accessory adrenal tissue may respond to trauma with increased activity. Clarification of these points will have to await the measurement of steroid activity and secretion in injured animals. It should also be pointed out that the particular response to injury which appears to be similar for the normal and the corticoid-maintained-adrenalectomized animal may be based on different metabolic mechanisms. The metabolic and functional significance of the increased levels of corticoids (hypercorticalism) after injury of the *intact animal* remains unclarified.

Considerably less information is available regarding the behavior of the other endocrine glands after injury and in shock. There is an *increased secretion of antidiuretic hormone (ADH)*, which doubtless affects renal function (Mirsky et al.). ADH liberation may be one of the mechanisms by which the secretion of ACTH is stimulated.

While the presence of active *thyroid hormone* seems necessary for the usual metabolic response to injury, knowledge of the behavior of the thyroid in shock is extremely limited.

Hamolsky et al reported an early progressive, but reversible, disturbance in the uptake of I^{131} by the thyroid of rats in tourniquet shock. Conversion to organic-bound iodine was slowed, reversibly, late in shock. They point out that these observations may represent either an increased or decreased thyroid activity. Similar changes were noted in tourniquet-shocked rats which had been adrenalectomized 3 weeks earlier and maintained on sodium chloride postoperatively.

One of the factors which obtunds generalization from experimental work to man *is the* wide species variation in hormone synthesis, secretion, excretion, and metabolism. *Furthermore*, the relationship between in vitro and in vivo hormone and gland studies is not always *clear*. The effects of extensive surgical procedures which are often required in in vivo endocrine studies also raise many questions An additional complication is the incomplete knowledge as to the effects of conjugation on the biologic activity of hormones, such that bioassay cannot equate a loss of potency with "inactivation." On the other hand, chemical quantitation may not describe the biologic activity of the material in question.

Finally, the orderliness of metabolism and activity of unicellular organisms, which (as far as is known) do not possess the counterparts of neurons or endocrines, should not be forgotten If, further, the fact is considered that an animal, properly cared for, may progressively adapt to the deficiencies created by ablation of portions of its nervous or endocrine faculties, its behavior and appearance seeming to be normal if the animal is not exposed to emergency situations, it becomes clear that "control" and "adaptive" modalities in higher organisms ultimately reside not in the highly specialized transmission and mediation systems (as they appear to under emergency situations), but in the peripheral tissues, more precisely, their cells and their "primitive" control mechanisms. In the higher organism, the regulatory influences of these keystones of homeostasis are abetted but masked by the superincumbent actions of the hormones and neurohumors (Levine, 1953, Krebs, 1955–1956) However, it has been amply demonstrated that the nervous and endocrine systems serve as "buffers" during emergency situations, functioning amidst reciprocal *interrelationships* to attenuate the latitude of adaptive *reactions*. (Selye, 1950, Ingle, 1951, Harris)

BIOLOGIC ENERGY TRANSFORMATIONS

The realization that the contribution of a burn or wound to an *ensuing* shock process is dynamic and protracted has led to much speculation and study on the nature of possible local factors, other than fluid and electrolyte shifts and losses, that might arise from regions of direct or secondary tissue damage and could cause adverse systemic effects, hastening the process to a fatal conclusion. It is somewhat *ironic* that an extract of skeletal muscle that on injection was reported (Green and Bielschowsky; Green, 1943) to reproduce the signs and symptoms of tourniquet shock, should ultimately prove to have its most deleterious activity ascribable to adenosine triphosphate (ATP).

ATP is one of the prime movers of normal biologic processes It is the chief energy carrier between energy-yielding catabolic reactions and the energy-requiring needs of cells. The aerobic energy-yielding metabolism of carbohydrates, fats, and proteins results in a coupled synthesis of ATP from inorganic orthophosphate and ADP (adenosine diphosphate), the *utilization* of ATP results in its breakdown to inorganic phosphorus and ADP. Intimately connected is the *creatine-phosphocreatinine* reaction (see Part 2, Chaps. 1 and 2)

The important role of ATP as an energy source on the one hand, and the evidence that "toxic" products from damaged or ischemic tissues might represent ATP or its breakdown products on the other, have led to studies which have examined both aspects in shock. Whether or not physiologically significant changes in plasma nucleotide concentrations occur in shock is still *uncertain*

Threlfall and Stoner (1957), who have been among the active investigators of this subject, have recently *stated* that "the absence of significant amounts of pharmacologically active nucleotides and their derivatives from the *blood* of the rat after limb ischemia helps *to* supply a negative answer to the question—do the adenine nucleotides play any part *in* the causation of the general responses to injury."

Hoffman et al., using a combined enzymatic and spectrophotometric *method* for determining ATP, ADP, and AMP (adenosine monophosphate), have assessed *these* adenine compounds in the blood of *patients* in various kinds of shock No significant changes in the blood levels of these compounds were found, nor were they detected in the serum. However, alterations *in the* ultraviolet absorption spectrum of the blood filtrates suggested that there was an increase in the blood level of a substance *closely related to the adenine* nucleotides, the addition *of* sodium inosine monophosphate to normal blood gave an abnormal spectrum exactly comparable to that found *in*

the cell; i.e., the ultrastructural and spatial organization may be of importance in the regulation of metabolic processes in the cell. This is particularly evident when the tissue slice or intact mitochondria is required to observe certain reactions. It is believed that the hormones may primarily influence cellular metabolism at this "enzyme-structure level" ("cytoskeleton" of Peters) instead of at the "enzyme level," the classical, more "primitive" method of control in which the vitamins, antimetabolites, and enzyme inhibitors apparently exert their influence on metabolism, and the level at which substrate and enzyme competition and the pure "biochemical lesion" are operative (Rossiter).

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Hamolsky et al. reported an early progressive, but reversible, disturbance in the uptake of I^{131} by the thyroid of rats in tourniquet shock. Conversion to organic-bound iodine was slowed, reversibly, late in shock. They point out that these observations may represent either an increased or decreased thyroid activity. Similar changes were noted in tourniquet-shocked rats which had been adrenalectomized 3 weeks earlier and maintained on sodium chloride postoperatively.

One of the factors which obtunds generalization from experimental work to man is the wide species variation in hormone synthesis, secretion, excretion, and metabolism. Furthermore, the relationship between in vitro and in vivo hormone and gland studies is not always clear The effects of extensive surgical procedures which are often required in in vivo endocrine studies also raise many questions An additional complication is the incomplete knowledge as to the effects of conjugation on the biologic activity of hormones, such that bioassay cannot equate a loss of potency with "inactivation" On the other hand, chemical quantitation may not describe the biologic activity of the material in question.

Finally, the orderliness of metabolism and activity of unicellular organisms, which (as far as is known) do not possess the counterparts of neurons or endocrines, should not be forgotten If, further, the fact is considered that an animal, properly cared for, may progressively adapt to the deficiencies created by ablation of portions of its nervous or endocrine faculties, its behavior and appearance seeming to be normal if the animal is not exposed to emergency situations, it becomes clear that "control" and "adaptive" modalities in higher organisms ultimately reside not in the highly specialized transmission and mediation systems (as they appear to under emergency situations), but in the peripheral tissues, more precisely, their cells and their "primitive" control mechanisms In the higher organism, the regulatory influences of these keystones of homeostasis are abetted but masked by the superincumbent actions of the hormones and neurohumors (Levine, 1953, Krebs, 1955–1956). However, it has been amply demonstrated that the nervous and endocrine systems serve as "buffers" during emergency situations, functioning amidst reciprocal interrelationships to attenuate the latitude of adaptive reactions (Selye 1950, Ingle, 1951; Harris.)

BIOLOGIC ENERGY TRANSFORMATIONS

The realization that the contribution of a burn or wound to an ensuing shock process is dynamic and protracted has led to much speculation and study on the nature of possible local factors, other than fluid and electrolyte shifts and losses, that might arise from regions of direct or secondary tissue damage and could cause adverse systemic effects, hastening the process to a fatal conclusion. It is somewhat ironic that an extract of skeletal muscle that on injection was reported (Green and Bielschowsky; Green, 1943) to reproduce the signs and symptoms of tourniquet shock, should ultimately prove to have its most deleterious activity ascribable to adenosine triphosphate (ATP).

ATP is one of the prime movers of normal biologic processes It is the chief energy carrier between energy-yielding catabolic reactions and the energy-requiring needs of cells. The aerobic energy-yielding metabolism of carbohydrates, fats, and proteins results in a coupled synthesis of ATP from inorganic orthophosphate and ADP (adenosine diphosphate); the utilization of ATP results in its breakdown to inorganic phosphorus and ADP. Intimately connected is the creatine-phosphocreatinine reaction (see Part 2, Chaps. 1 and 2).

The important role of ATP as an energy source on the one hand, and the evidence that "toxic" products from damaged or ischemic tissues might represent ATP or its breakdown products on the other, have led to studies which have examined both aspects in shock. Whether or not physiologically *significant* changes in plasma nucleotide concentrations occur in shock is still uncertain.

Threlfall and Stoner (1957), who have been among the active investigators of this subject, have recently stated that "the absence of significant amounts of pharmacologically active nucleotides and their derivatives from the blood of the rat after limb ischemia helps to supply a negative answer to the question—do the adenine nucleotides play any part in the causation of the general responses to injury."

Hoffman et al, using a combined enzymatic and spectrophotometric method for determining ATP, ADP, and AMP (adenosine monophosphate), have assessed these adenine compounds in the blood of patients in various kinds of shock. No significant changes in the blood levels of these compounds were found, nor were they detected in the serum However, alterations in the ultraviolet absorption spectrum of the blood filtrates suggested that there was an increase in the blood level of a substance closely related to the adenine nucleotides, the addition of sodium inosine monophosphate to normal blood gave an abnormal spectrum exactly comparable to that found in

patients with severe shock. Others have found some increases in plasma uric acid concentrations in shock

Measurements of muscle ATP contents have shown significant decreases in the directly damaged muscles in conditions such as tourniquet shock, but the evidence is controversial regarding other muscles of shocked animals. Following limb ischemia in rats, it has been found that the restoration of energy-rich phosphate levels in muscle appears to depend not only on the duration of ischemia, but also on the degree to which circulation is restored following release of occlusion. If the limb is ischemic for more than 2 hr, inorganic phosphate and nucleotide disappear from the damaged muscle Although the fate of the nucleotide has not been established, it is believed that it is released from the muscle as inosine monophosphate (Threlfall et al, 1957). This would appear to tie in with the observations already mentioned of the abnormal ultraviolet absorption spectrums (possibly ascribable to inosine) of blood filtrates of patients in shock

Extensive investigations were performed on biologic energy transformations in hemorrhagic, tourniquet, and Noble-Collip drum shock in rats (McShan et al., LePage) They found generally decreased tissue levels of high-energy phosphate compounds and energy-yielding substrates, they also noted increased blood levels of certain pentoses, inorganic phosphorus, and products of protein and carbohydrate catabolism Following hemorrhage in rats, the liver and kidneys seemed to be most affected, whereas brain, heart, and skeletal muscle energy stores were less affected, the changes in Noble-Collip drum shock were comparable to that of hemorrhage, but those following tourniquet shock were less severe

They interpreted their data as consistent with their hypothesis that *the state of shock, in general, involves a critical depletion of energy reservoirs (ATP and phosphocreatine)* Depending on the type of shock (*initiating* cause), they hypothesized that there may be *either a primary breakdown (as by "overwhelming stimulation," e.g, Noble-Collip drum shock), a failure of resynthesis of high-energy compounds (hemorrhage), or a combination of both (tourniquet shock).*

During *hemorrhagic shock* in dogs, the "high-energy phosphate" content of liver is found to decrease. However, the extent of the decrease does not correlate with the ultimate response (favorable or unfavorable) of the dog to transfusion of the shed blood (Rosenbaum et al.). Whether or not dogs survive following transfusion, the hepatic pyrophosphate level is rebuilt to the extent that arterial pressure has improved at the time the liver sample is taken. These findings are in general agreement with those previously mentioned regarding the rapid restoration of normal blood levels of lactate, pyruvate, and amino acid metabolism following transfusion after oligemic shock in dogs.

It has been suggested that the generalized depletion of energy-yielding compounds, if present, results either from an "uncoupling" of oxidation from phosphorylation (i.e, failure to synthesize "high-energy" bonds while carbohydrates, etc., are still being broken down) or from an incomplete metabolism of carbohydrate. However, Stoner et al. (1952b), found that when an uncoupling agent—dinitro-*o*-cresol—is injected into rats, there result chemical and physiologic effects unlike those of tourniquet shock. Regarding the theory of incomplete breakdown of carbohydrate, there are insufficient data on hand from studies of various forms of shock to draw definite conclusions Although it is tempting to speculate that there is a "block" in carbohydrate catabolism between the glycolytic and tricarboxylic acid cycles in view of the reported unique increase in glucose-6-phosphate in undamaged muscle of rats in tourniquet shock, this might only reflect the generalized increased rate of carbohydrate breakdown (Threlfall et al., 1954).

Judging from the injection of a wide spectrum of tissue metabolites (potassium, magnesium, calcium, inorganic phosphate, adenine, adenosine, adenylic acid, ATP, histamine, tyramine, and acetylcholine), Tabor and Rosenthal felt it unlikely that the temperature fall observed following tourniquet release is due to the release of these materials into the circulation in shock. Although magnesium and ATP can lower body temperature, the amounts required apparently exceed those present in the tissues Several other studies (Stoner et al, 1954, Coranson et al.) have not supported the generalized "energy-depletion" hypothesis of shock.

Limb ischemia (tourniquet) in rats kept in a room at about 20°C did not cause significant changes in the energy-rich phosphate concentration of muscle outside the damaged area; turnover rates of ATP and phosphocreatine were not altered significantly outside the damaged limbs Stoner and Threlfall felt that the fall in body

temperature decreases the energy demand, resulting in a temporary balance between production and utilization of energy-rich bonds which allows the animal to survive for an extended period of time. However, at higher environmental temperatures, 30°C, a generalized tissue depletion of high-energy materials was found during fatal limb ischemia Stoner and Threlfall suggested that the elevated environmental temperature prevents the fall in body temperature that usually ensues in tourniquet shock, and as a consequence, energy production is not so severely depressed However, the energy requirement appears to be disproportionately increased, since survival time is shortened and the decrease in tissue high-energy phosphorus is exaggerated.

The findings to date, primarily because of limitations of technique, have neither proved nor disproved the possibility that depletion of energy stores of certain vital cells might be responsible for death from shock
(Green et al, 1954.)

OXYGEN CONSUMPTION, ACID-BASE BALANCE, ENZYMES, AND VITAMINS

Oxygen consumption is generally lowered in severe shock This reflects primarily the slowed blood flow, the tissues apparently do not lose their ability to use oxygen until the terminal stage However, functional and anatomic deterioration may set in before oxygen consumption fails quantitatively (as judged principally by in vitro studies) This has been demonstrated for dog brain by Rosenthal, O, et al (1945).

Consequent to the inadequate oxygen and nutrient delivery and slowed venous blood flow in shock, a *metabolic acidosis* results, there are a decrease in blood pH, carbon dioxide, and bicarbonate contents, and increases in pyruvate, lactate, phosphate, and sulfate Pulmonary ventilation or diffusion changes may alter this pattern, at times a *respiratory alkalosis with hypoxemia* may result *Renal blood flow is sharply curtailed*, and urinary output slows and finally stops, thereby, the regulating effects of the kidneys on acid-base balance are lost to the severely shocked individual

The liver has been the most frequently studied tissue in shock Considerable disagreement exists as to whether liver respiration is increased or decreased in shock Most of the information derives from in vitro studies However, many of the apparent differences are reconcilable when consideration is given to the details of the individual experiments and the type of shock procedure used.

An explanation for some of the apparently conflicting findings is offered by Hannon and Cook. They subjected rats to either tourniquet or hemorrhagic shock and demonstrated that liver taken during the "terminal stages of shock" could have either high or low rates of oxygen consumption, depending on the preshock nutritional state of the animal. They confirmed the work of Fuhrman and Field by demonstrating that a depletion of liver glycogen by fasting the normal animal results in an apparent increase in in vitro liver oxygen consumption, as was the case when liver glycogen depletion resulted (presumably from hypoxia) following tourniquet, freezing, or burn shock in the previously well-fed rat. However, they point out that "the observed Q_{O_2} for shocked tissue is not comparable with the normal tissue since the methods of calculation do not take into account the increment of weight added to the normal tissue (or subtracted from the shocked tissue) by the glycogen present" When this is accounted for, no differences are noted between the livers of the controls or shocked animals except when the shocked rats had been deprived of water and food for 24 to 30 hr. They conclude: "We may now regard shock as being either of no influence or conducive to a reduction in respiration, this effect being primarily referable to the stagnant anoxia occurring in the liver. The degree of reduction, if any, would in turn be determined by the severity of the anoxia together with the magnitude of the initial energy stores." They suggest that a structural or chemical derangement in the mitochondria of liver tissue (secondary to hepatic hypoxia and an ensuing depletion of high energy phosphate) may be the basis for certain of the observed biochemical changes

Wiggers has found in his studies of experimental hemorrhagic shock in dogs that despite evidence of compensatory mechanisms which tend to support coronary circulation, *myocardial depression ("deterioration of myocardial expulsive power") may occur during oligemia, which may contribute to the progressive circulatory failure at this time*, while transfusions prove to be of temporary benefit only These findings were based primarily on cardiac pressure and volume curves He made it clear that although his evidence suggested that myocardial depression is a "frequent and important complication," it might not be a factor in all

states of shock, and its severity would be conditioned by the variations in the preshock functional status of the myocardium (muscle and vessels) of patients or experimental animals.

Bing emphasized that the normal, relatively low coronary flow (8 per cent of the cardiac output) is counterbalanced by the maximal myocardial oxygen extraction. He points out that *in hemorrhagic shock, the fall in oxygen usage by the heart is due not to reduction of myocardial oxygen extraction but to the reduction in coronary flow*

The observations of Edwards et al. suggest that *hypoxia of the heart,* apparently unlike that of other organs, results in an increased extraction (utilization is not changed because of the reduced coronary blood flow in shock) of lactate; this suggests that the enzymatic pathways for lactate metabolism are not deranged consequent to the myocardial ischemia of hemorrhagic shock. The tendency toward negative myocardial glucose and pyruvate balances suggests that there may be a block in their metabolism Although the investigators did not measure cocarboxylase (phosphorylated thiamin), they suggested that dephosphorylation of the latter, which has been reported to occur in various tissues (other than the heart) in hemorrhagic shock and anoxic anoxia by Grieg and Govier, may be the primary factor preventing pyruvate catabolism via the tricarboxylic acid cycle. However, this hypothesis, at the same time, renders the fate of myocardial lactate uncertain, since its catabolism via this pathway would likewise be blocked.

Strawitz and Hift found that the mitochondria of hearts, livers, and kidneys from dogs in hemorrhagic shock differed in size and shape from those of normal dogs. Heart mitochondria, isolated by differential centrifugation, from the shocked dog retained the normal oxidative capacities for Krebs cycle substrates. However, in the presence of the hexokinase system (which imposes a constant extramitochondrial demand for ATP) heart mitochondria from the shocked dogs manifested impaired oxidative capacities The latter led the author to make an interesting suggestion "It is possible that the classical Warburg methods, which supply an optimal environment as far as cofactors and substrate requirements are concerned, obscure or reverse early enzymatic defects."

There is a surprising lack of information on the metabolism of the various water- and fat-soluble *vitamins* in shock, and of the enzymes for which some of these vitamins in modified form are cofactors (coenzymes). That information which is available is conflicting and rife with uncertainty. The possible derangement of vitamin and enzyme functions (coenzyme, apoenzyme, or both) consequent to the hypoxia and related sequelae of shock, and its possible early relevance to the metabolic responses already detailed, are clearly of fundamental interest—thiamin, pantothenic acid, pyridoxine, nicotinamide, and riboflavin are functionally interrelated in hormone, carbohydrate, lipid, and amino acid metabolism, and in cellular respiration (hydrogen carriers). The inadequacy or cumbersomeness of the analytic methods used and the prevalent uncertainties of the specific actions of and requirements for the various vitamins in the normal individual, to say nothing of the injured person, probably have been the primary deterrents to their intensive investigation in shock "That symptoms of vitamin deficiency result from partial failure of one or more metabolic functions for which the missing vitamin is essential is a truism It is an interesting commentary on the present state of our knowledge, therefore, that in almost no instance is it possible in higher animals to correlate the presence of a given symptom of vitamin deficiency with hypofunction of a known enzymatic reaction for which that vitamin is essential Until this becomes possible, our knowledge of the relationship of these bodily catalysts to physiological function is incomplete" (Snell).

Soon after shock there is an abrupt and often sustained drop in blood and urinary *ascorbic acid,* and an apparent decrease in tissue ascorbic acid saturation, as judged by "load tests" In the rat, ACTH-stimulated secretion of ascorbic acid from the adrenal gland into the adrenal venous effluent precedes the release of corticosterone, the ascorbic acid discharged by the adrenal gland can be quantitatively recovered from the adrenal venous effluent (Slusher et al.). The basis for the lowered tissue saturation and plasma content of ascorbic acid is not known

Many shock studies have been performed with ascorbic acid pretreatment. Whereas guinea pigs (which, like man, require a dietary source of vitamin C) that were pretreated with large doses of ascorbic acid before being subjected to a standardized hemorrhagic shock procedure showed a significant increase in survival rate (de Pasqualini), no beneficial effects were noted in ascorbic acid–primed rats subjected to hemorrhagic shock

(Sayers, G., et al., 1945). Ascorbic acid given to mice after the release of tourniquets also had no significant effect on survival (Millican et al.)

Certain vitamins may be active only when combined as *coenzymes*. This implies that a plethora of "free" vitamins does not exclude a possible deficiency of coenzyme It also seems reasonable that the hypoxia and hyponutrition of the tissues in shock may result in a "functional" derangement and altered metabolism of certain *enzymes* and enzyme systems Furthermore, known ionic imbalances (specifically required metallic ions), pH, and fluid shifts may contribute to enzymic alterations during shock.

Lamson et al. were brought to the problem of studying certain coenzymes and their associated vitamins in shock by their earlier findings of liver glycogen depletion and the inability of insulin to alter the glycogenolysis and hyperglycemia of shocked dogs They were aware of the carbohydrate disturbances accompanying thiamine deficiency and a reported effectiveness of thiamine therapy in severely burned patients Dogs were subjected to fractional hemorrhage to a low level of arterial pressure with no replacement therapy, generally, control dogs died in 3 to 4 hr from the start of bleeding It is unfortunate that these experiments were not supplemented by other types of hemorrhagic shock procedures, particularly those with reinfusion of the shed blood These workers first found that thiamine administration results in a fall in blood pyruvate (keto acids) and an increase of both the blood pressure and survival times They next found that the pyrophosphate ester of thiamine, cocarboxylase, was being dephosphorylated in skeletal muscle, duodenum, and liver, chiefly in the former two tissues However, while Alexander, who studied the free and phosphorylated (total) thiamine content of dog liver and muscle under different experimental conditions of hemorrhage, found a decrease of muscle cocarboxylase, he found, on the contrary, an increase in total and phosphorylated thiamine in the liver (Alexander's dogs were given extra thiamine for 2 to 4 days prior to bleeding) Greig further found that vitamin-containing coenzymes, such as cozymase (nicotinamide) and alloxazine adenine dinucleotide (riboflavin), were decreased in brain, muscle, and liver (in this order) after hemorrhage, more consistent reductions being observed with cozymase, and that the apoenzymes were also possibly being inactivated, since in vitro studies indicated that the apoenzymes of lactic dehydrogenase and amino acid oxidase were destroyed under anaerobic conditions

Although the relationship between in vitro and in vivo studies is not always apparent, it has been demonstrated that, in contrast to the above findings, the addition of thiamine or cocarboxylase to a homogenate of brain tissue after hypoxia did not result in improvement of the decarboxylation of pyruvate. This was taken to indicate that *neither destruction of the respiratory enzymes nor a critical deficiency of coenzymes is a primary result of hypoxia* (Rosenthal, O., et al.). Increased *proteolytic* and *fibrinolytic* activity in the blood and plasma of animals and patients may occur when shock is severe and prolonged; the physiologic significance of these changes is not known.

Shorr et al have demonstrated that two humoral vasotropic principles, one *a vasoexcitor material* (VEM) and the other *a vasodepressor material* (VDM), appear in successive order during experimental hemorrhagic, traumatic (Noble-Collip drum), and tourniquet shock.

The presence of these materials was recognized by a bioassay technique which involves the microscopic detection of a VDM or VEM response of the terminal vascular bed of the mesentery of the rat's mesoappendix to topically applied epinephrine after intravenous injection of the test material, usually blood or incubation medium. The appearance (titer) of these vasotropic factors in the blood of shocked animals has been temporally correlated with direct visual observations of the successive hyper- (compensatory stage) and hyporeactive (decompensatory stage) phases of the terminal vascular bed of the mesentery.

TOXINS, TOXEMIA, AND INFECTION

Cannon and Bayliss and Dale et al. (1918) presented evidence that shock following muscle injury might be due to the absorption of one or more toxic substances formed in the injured muscle *The toxin theory of shock,* with its implied humoral vector, has remained a most provocative subject. Certain investigators have not been deterred from espousing the idea that a single "toxic" factor may be the *cause* or the *predominant cause* of shock, hoping to find a simple preventive or cure for shock However, present awareness of the multietiologic nature of the shock syndrome and its variable complex of possible sustaining and perpetuating factors, which are often clinically recognizable,

has provoked the statement that ". . . the search for a simple method of treating shock is akin to the search for the fountain of youth —it is a phantasma" (Moyer, C. A., 1953).

The nature of VEM, which appears very early in shock and which derives from the hypoxic kidney, is unknown; its vasoexcitor property, however, can be abolished in vitro by liver or kidney tissue. Prolonged hypoxia renders the kidney incapable of producing VEM further, and for this reason, it may cease to appear in the blood late in shock. VDM has been identified as a form of *ferritin*, an iron-containing protein normally found in many tissues (primarily liver, spleen, skeletal muscle, and duodenal mucosa), that has vasodepressor activity, which property can be inactivated aerobically or activated anaerobically in vitro by liver tissue. It is believed that the prolonged hypoxia of shock also results in its release in vivo, peak titers are noted during the decompensatory stage. Its persistence in the blood is believed to result from the progressive hypoxic deterioration of the poorly characterized liver-inactivating mechanism.

Some reports question the importance of VDM in the shock syndrome (Hampton et al ; Frank, H. A., et al , 1952b) However, there is presently no decisive evidence that VDM is or is not causally related to the "irreversibility" of shock. Shorr's colleagues are currently pursuing the study of the metabolism of ferritin, and the activation and inactivation of its vasodepressor properties by liver parenchymal and reticuloendothelial cells (Baez et al.). The *reticuloendothelial system* has recently gained new prominence in its apparent relationship to the shock syndrome, but the nature and details of its participation are yet to come.

A most interesting and unique finding is the ability of the liver of Noble-Collip drum–tolerant animals to inactivate VDM aerobically in vitro after it has previously been exposed for 2 hr of anoxia in vitro, which regularly destroys the inactivating capabilities of normal rat liver (Zweifach et al , 1951) *Tolerance* was established by subjecting the animals to graded and repeated episodes of trauma, they thereby became resistant to ordinarily lethal doses of such trauma Such animals exhibit certain metabolic changes during the training regimen, e g , decreased liver glycogen and decreased body fat (Chytil et al.), and may have a cross tolerance for other types of trauma, e.g , hemorrhage. Following exposure to trauma, they manifest biochemical changes of tissue and blood that are qualitatively similar to those of nonadapted animals, but, in contrast to the latter, the rate and degree of these alterations, in general, are not so great, and, most importantly, they tend to be restored to normal more quickly

Further exploration of the mysteries of adaptation to injury and shock are in order and are needed before any description of mechanisms can safely be made.

There is some evidence that animals have a lowered resistance to infection and an increased susceptibility to injected endotoxins in the early period after severe injury, particularly if shock is present or has occurred The mechanisms for these alterations in sensitivity are not yet known. An abrupt drop in the serum properdin level and some alterations in reticuloendothelial function have been noted, as well as the numerous metabolic changes already described. Dubos, describing some of his observations of experimental infection in animals subjected to abrupt changes in dietary intake, has stated:

> It is likely that disturbances in the general state of health often bring about qualitative and quantitative changes in the biochemical characteristics of the inflammatory area. These in turn may interfere with the processes which control the activities of micro-organisms within the lesion As a result, the response of the body to infection and consequently the micro-environment in which the infectious process follows its course, are under the control of factors which may be metabolic or psychic in origin. This concept accounts in part for the fact that susceptibility to infection can change independently of the immunological state of the infected individual. Since changes in susceptibility can occur rapidly, and be extremely transient the intensity of exposure to an infectious agent may be less decisive than the physiological state of the exposed individual, determining whether infection fails to take hold, becomes established, runs an abortive course, or evolves into overt diseases.

If fulminating infection develops in the injured patient or animal, shock may thereby be induced or, if present, intensified, e g , the severe circulatory failure secondary to the toxemia of clostridial wound infections. But what of the possibility of toxemias not so patently present?

Fine and coworkers have submitted a large

body of experimentation on several species and forms of shock, especially shock irreversible to blood transfusion, which they are satisfied indicates that a toxic humoral factor, viz., a bacterial endotoxin deriving from the bacteria of the gut, plays a predominant, if not exclusive, role in determining the lethality of shock They have demonstrated to their satisfaction that blood or Seitz-filtered plasma of animals (rabbits and dogs) dying of irreversible hemorrhagic shock can kill suitably sensitized recipient animals, but not normal animals, on parenteral injection (Fine, Schweinburg et al., 1951) These findings are as yet uncorroborated One of the authors of this chapter (Einheber) has not been able to find toxicity in the blood of dogs and rabbits dying of irreversible hemorrhagic shock or of rabbits dying in a shocklike state following temporary occlusion of the superior mesenteric artery (see Shock in General, earlier in this chapter).

CONCLUSION

Some factors clearly involved in the metabolic changes associated with shock have been discussed, and some of the limited information regarding their pertinence has been presented Unfortunately, most of the reports have been concerned with changes in concentration of various metabolites in blood and plasma There have been few in vivo measurements of specific tissue metabolism. Interpretation of the blood chemical changes is complicated by the factor of differential circulation rates per se, superimposed on the possible changes in the metabolism of the organs or tissues involved Since many of the qualitative biochemical alterations found in shock are likewise observed after injury *without* shock, the precise significance of these alterations as regards the ultimate fate of the individual are incompletely known and remain largely speculative The same holds true for the basic mechanisms responsible for the evolution and progression of these alterations. At the same time, one should not lose sight of those metabolites which seemingly are not altered "Thus we might assume as a working hypothesis, that whatever variable is held most constant is the key to natural physiologic regulation The wisdom of the body is such that by the time a steady state is reached, under new demands, the important variable, the one with survival value, is regulated within physiologic limits" (Hamilton).

At present, it would seem, as Engel wrote (1953),

> that a variety of metabolic changes eventuate as a result of the hypoxia of circulatory failure, and that in general these reflect a shift to an anaerobic type of metabolism, with consequent decrease in efficiency in terms of energy yield. This latter fact in itself might be considered as the most important consequence of the initial hypoxia, and if uncorrected might be expected to lead to increasing deterioration of many essential systems and functions which are dependent on a continuing energy supply. At what point these summated changes and energy deficits become critical remains to be established

In determining the pertinence of various observations, particularly with a view to establishing their role in the lethality of the shock state, the following should be considered: If the correction of a trauma-induced "deficiency" (excluding obviation of positive deleterious factors at injury) is attempted some time after injury and results in the survival of the animal, then it is important to be able to recognize the stage after injury when a particular animal or a majority of animals in a group will no longer respond to such corrective measures, assuming that the effectiveness of such measures is shown, in general, to diminish with the time elapsing after the initiation of injury, e g, blood transfusion in hemorrhagic shock If such a prediction of lethal outcome cannot reliably be made because of inadequate objective criteria or because replacement therapy is not attempted or is inadequate, or the animal dies or is sacrificed prematurely, then the death of the traumatized animal or the associated phenomena studied (observed manifestations) may be due to a deficiency of the effective therapeutic agent (e g, whole blood, plasma, or electrolytes), or to such a deficiency plus its consequences (i e, those derangements no longer remedied by replacement therapy as judged by death).

The authors have high hopes that new approaches to "shock problems," made possible by the use of some of the recently developed scientific techniques and the recognition of the induction of resistance to noxae by "conditioning," will provide some answers to fundamental questions which plague physicians and researchers today.

1

Arteriosclerosis

J. LINZBACH

Lobstein (1833) coined the word *arteriosclerosis* for the changes consisting of thickening and induration of the layers of the arterial wall Histologically it is possible to observe completely different morphological changes in the affected arterial walls. There are hyperplastic, degenerative, thesaurismotic, necrotic, inflammatory, and organizing productive processes that can occur in any combination (Wolffe et al, 1952)

During the intervening time, it has been found impossible to determine a common pathogenetic explanation for the different morphological observations or to distinguish certain types of arteriosclerosis etiologically, pathogenetically, or morphologically unless certain inflammatory and degenerative arterial diseases were taken into consideration

Almost every case differs from others by quantitative, qualitative, and local variations One extreme is formed by cases of so-called *diffuse arteriosclerosis* in which it is sometimes possible to study the complete morphology of arteriosclerosis The other is represented by cases in which a single, isolated plaque, located on the intima of a coronary vessel and weighing only a few milligrams, is responsible for death This variability and the "focal" character of the disease indicate different pathogenetic mechanisms acting during life, among which are physical and chemical properties of the vascular wall and of the blood In spite of the fact that most people die from the effects of arteriosclerosis, the mechanism of this disease is still unknown. All the pathogenetic theories on human arteriosclerosis are based upon either experiments with animals, or circumstantial evidence from morphological observations A pathogenetic hypothesis has to consider that arteriosclerosis (1) is focal; (2) increases with age, (3) is combined with various morphological changes; (4) has a predilection for determined points of the same vessel, (5) is found in men earlier than in women, (6) is found more commonly and at an earlier age in strong, muscular persons, (7) is accelerated by high blood pressure, (8) is promoted by certain metabolic disturbances (see also experimental arteriosclerosis); (9) occurs during infectious or toxic states, and (10) is very rare and of moderate degree in the pulmonary artery and in veins.

THE NORMAL ARTERIAL SYSTEM

Structure. The vessels and the heart are lined with a continuous and *uninterrupted endothelial layer* Using a light microscope it is possible to observe, in freshly fixed material from human beings, an endothelial layer in the whole aorta, the large and middle-sized arteries, and the veins [Linzbach et al, 1957 (*man*), Duff et al, 1951 (rabbit).] In fresh preparations of the aortic intima of both man and various mammalians it is possible to observe with the phase-contrast microscope that the endothelium is supported by cytoplasm at the side opposite to that of the blood stream (Fig. 15-1) For this reason fresh endothelia, consisting of only one layer of cells, have amazing strength and elasticity, and can stand a certain amount of tension (Linzbach, 1952). Even at the highest magnifications it is not possible to recognize an intercellular cementing substance which binds the endothelia to-

corresponds to the effective filtration pressure in this layer.

Functional Anatomy. The arterial wall can be compared with a combination of a car tire with and without an inner tube (Linzbach, 1958). The inner tube corresponds to the endothelium, the most internal layer of which is plastic, deformable cytoplasm, while the reticular external layer is porous (Fig. 15-1) and is supported by a plastic viscous layer (subendothelial connective tissue). The musculoelastic media corresponds to the tire and the lamina elastica interna of the muscular arteries to the inner tube, which can be distended only with difficulty.

When one considers the arterial system from this point of view, the following proportion appears While *the blood pressure decreases to one-third from the aorta to the capillaries, the diameter increases about 10,000 times* The total wall *tension must* then be 10,000 times larger than in a capillary (Burton, 1951). (Aorta *tension* = 150,000 dynes/cm; capillary *tension* = 12 dynes/cm.)

The morphological nature of the endothelium proves that the wall tension in this layer is of the same order in both the capillary and aorta In the capillaries, a blood pressure of 30 mm Hg, with a tension in the endothelial layer of 12 dynes/cm (equivalent to 12 mg/cm), is tolerated well and produces an equivalent filtration pressure in the endothelial layers, this is not possible in the arteries An endothelial tension of 12 dynes in the arteries represents only a minimal fraction of the level of blood pressure. However, the filtration pressure in the endothelium of the arteries must still be small It follows that the elastic viscous endothelium and the subendothelial connective tissue are compressed against the solid internal layers of the media by almost the entire intravascular pressure in the arteries Therefore, the hydrostatic pressure in the intima must decrease from the aorta to the periphery The exact level of this compression depends upon both the intravascular pressure and the elasticity of the internal layers of the media and of the lamina elastica interna, respectively As the intravascular pressure decreases in the arteries from the center to the periphery, a corresponding longitudinal pressure gradient must exist in the intima. This is of an order of magnitude which corresponds approximately to the decrease in pressure within the arteries Although the pressure drop, and therefore the longitudinal pressure gradient are small in comparison with the length of the arterial system, these forces are sufficient to produce, during life, a slow but constant *peripheral displacement of fluid in the intima*, i e, from the thoracic to the abdominal aorta and also within the peripheral vessels This longitudinal flow in the intima can be accelerated in the aorta by the pulsational variations in pressure.

In the capillaries, the intravascular pressure produces a high filtration pressure. *In the aorta and other arteries, on the other hand, there is high compression and low filtration pressure* The compressive force on the human aorta corresponds to a load of about fifty kilograms. As the colloid osmotic *pressure of the blood is only about* 25 mm Hg, the low filtration pressure *in the* arterial endothelium with *the endothelium* under high compression is of great *importance* to the internal tightness (Linzbach, 1958).

Although the vascular diameter increases *10,000 times, from the capillaries* to the aorta, the thickness *of the* wall increases only about 1,000 times *from* the capillaries (about 2 to 3 μ) *to the aorta* (2 to 3 mm). Consequently, the parietal tensions exerted on the wall (Eq. 3) and the density of the constituent materials *must* be 10 times greater in the tunica *externa* (tire) than in the intima (inner tube).

In agreement with Burton (1951), it is *necessary* to admit that the brunt of the tension of the arterial wall is sustained by the elastic material, with a *relative* decrease from the aorta to the periphery. The modulus of elasticity of the elastic fibers has been evaluated as 1.4×10^7 dynes/cm² by Meyer et al. (1950), while the value *obtained* from the protein content of muscle fibrils amounts only to 0.8×10^7 dynes/cm² and, considering the water content of the muscle, should be essentially *still* lower.

Nutrition of the Vascular Wall. The normal structure and function of a tissue presupposes adequate nutrition Warburg (1926) developed the concept of *critical* "layer-thickness" of tissues. This term defines the *maximum* thickness which a tissue *between* two nourishing surfaces (e g, between two capillaries) may attain so that the supply of nutrient substances



Fig. 15-1. Model of the endothelium of the human aorta. The model was sketched following studies with the electron microscope of fresh, unfixed endothelial preparations.

gether and in which metabolic changes occur (Chambers et al, 1947). However, it is not possible to demonstrate pores with the light microscope.

At the side adjacent to the blood stream, the cytoplasm of the endothelial cells forms hyaloplasmic pads of variable height which can be designated as covering plates. The borders of these plates lie closely together and form (under the phase-contrast microscope) a framework which meets with the cell boundaries and the places of silver lining (Fig. 15-1). The healthy *subendothelial connective tissue* contains fine collagen and elastic fibers. The ground substance is impregnated with acid mucopolysaccharides. Besides, there are fibrocytes, histiocytes, and monocytes (Duff et al, 1957); and also many mast cells (Sundberg, 1955), which are important in heparin formation that may play a role in the stability of the fat in the ground substance of the intima. From the physical point of view, it is possible to consider the healthy subendothelial connective tissue as a *loose, elastic viscous sponge*.

In muscular arteries there is a strongly woven, tough membrane, the *lamina elastica interna,* between the muscular *media* and the subendothelial connective tissue. It forms an elastic perforated tube, which is strengthened by lengthwise and crosswise fibers. In the cerebral arteries, the lamina elastica interna is particularly well developed. The musculoelastic media of the aorta, on the other hand, has no internal elastic membrane.

The Relationship between Blood Pressure, Elasticity, Wall Tension, Compression (Intramural Pressure), and Filtration Pressure. The intravascular blood pressure (p) in dynes per square centimeter produces a tension (F) in dynes (Fig. 15-2).

$$F = p \cdot 2r \cdot l \qquad \frac{\text{dynes}}{\text{cm}^2}\,\text{cm}\cdot\text{cm} \qquad (1)$$

where r = radius

l = length of vessel

The elasticity produces (in the wall of the vessel) a tangential tension of the wall. It is measured by the formula of Laplace as total wall tension (T_r) in dynes per centimeter along the length of vessel.

$$T_r \approx p\,\frac{2rl}{2l} = p \cdot r \qquad \frac{\text{dynes}}{\text{cm}^2}\cdot\text{cm} \qquad (2)$$

The wall tension (T) in dynes per square centimeter corresponding to the thickness of the wall of the vessel (S), has the dimensions of a pressure, and it is possible to calculate it from the elasticity (F), divided by the measure of both diameters (inner and outer) of the vascular wall (Fig. 15-2).

$$T = p\,\frac{2rl}{2dl} \approx \frac{pr}{d} \qquad \frac{\text{dyne}\cdot\text{cm}}{\text{cm}^2\ \text{cm}} \qquad (3)$$

These equations are valid only for vessels with relatively thin walls.

In arteries with thick walls consisting of multiple elastic layers, the first internal layer transforms part of the blood pressure into wall tension. Its external layer, therefore, will not be compressed against the internal surface of the second layer by the full blood pressure. As every layer absorbs part of the blood pressure in the form of wall tension, the compression of the layers of the wall will decrease *from the inside out.* The thicker the layer, the larger *is its modulus* of elasticity, and the greater the percentage of blood pressure which will be *transformed into* wall tension, with greater decrease of compression. This decrease

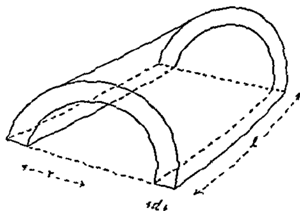


Fig. 15-2. Explanation in the text.

coronaries, others in the media, i.e., the femoral arteries (Hieronymi, 1956). In persons with hypertension, the thickening of the wall is more rapid. Focal and diffuse fibrotic thickenings of the intima occur in many arteries at very typical points without any simultaneous deposit of lipids.

EARLY CHANGES

Diffuse and Focal Lipid-free Fibrous Thickening of the Intima. The theory of gradients of pressure in different directions in the intima, caused by the intravascular pressure, can explain the formation and localization of the thickenings of the intima

1. Thickening of the intima develops more rapidly in the abdominal than in the thoracic aorta (Wilens, 1951)

Explanation: A gradient of pressure with centrifugal direction produces a slow current of filtration that causes a chronic "edema of the intima" in the abdominal aorta. This is gradually and continually transformed into the "edema-sclerosis" of Rossle (1943)

2. At the bifurcation of the aorta, there are fibrous thickenings of the intima

Explanation. The drop in blood pressure which takes place in the branches causes a displacement of the tissue fluid of the intima in the branches of the aorta.

3. In tortuous arteries, the intima is thicker at the internal than at the external part of the curves

Explanation In a curved vessel, the intravascular pressure is higher toward the outer than toward the inner border Therefore, a circular gradient of pressure is created with an accumulation of tissue fluid, followed by a proliferation of intima in the areas of minimal pressure on the inner curvature

4. At points which are pathologically narrow, as in coarctation of the aorta, there are thick, fibrous plaques on the intima

Explanation At the point of coarctation, the arterial pressure drops, however, it increases again below the stenosis The plaques form at the points of low pressure In this connection, one should also remember the formation of *endocardial plaques* from the cardiac jelly in the narrow atrioventricular canal

In spite of the fact that the thickness of the arterial walls increases continually, additional vascularization of the media can be shown in men about 30, and in women about 40 years old (Linzbach, 1944).

Qualitative Early Changes in the Intima. The so-called *lipoid spots* represent slightly elevated, yellowish, pin-point, or longitudinally striped thickening of the intima. They are found even in sucklings, especially in the intima of the thoracic aorta In young people they are usually reversible. Their formation seems to depend upon the content of fat in the diet, and subsequently of the blood (Zinserling, 1925, Bragdon, 1952, Duff et al., 1935–1954). The small foci contain fat and lipids Droplets of fat are seldom seen in the endothelium. How fat deposits in the intima from the blood and why the deposits are formed are unknown Leary's theory (1949) postulates that reticuloendothelial cells containing fat, i.e., those mobilized in the liver, are carried with the blood stream in the aorta and then penetrate through the endothelium in the intima, this has been proved wrong by isotope studies (Simonton et al., 1951) The longitudinally striped arrangement is in favor of the theory of Wilens (1942) that the fat is not only deposited at the points of entry into the intima but can wander within this structure. Presumably, the pressure gradients in the intima determine the direction of this movement The splitting and fracturing of the lamina elastica interna starts with simultaneous elastic fibrous thickening of the intima of the coronary arteries in infancy (Wolkoff, 1923, Dock, 1946; Lindsay et al., 1952, Paterson, 1952, Schornagel, 1956). After the age of twenty, fracture of the split lamina interna of the femoral arteries is also the rule (Linzbach, 1944) There is abundant mucoid material within the split lamina. The elastic fragments are often surrounded by calcium The same changes, though less marked, occur in the arteries of the arm. In the thick lamina elastica interna of the cerebral arteries the fracture begins only in the fourth decade (Wolkoff, 1933) Starting in the second decade of life, it is already possible to demonstrate an increasing deposition of acid mucopolysaccharides in the *media* together with fine, dusty calcification of the intercellular substance Loosening and fracture of the internal elastic lamina of the aorta with destruction of muscle fibers has been shown in thickenings of the intima (Taylor, 1951).

and oxygen and the elimination of products of metabolism will always be sufficient for the structural and functional requirements. The critical layer-thickness decreases proportionally as the cellular metabolism rate and the density of the cell population of a tissue increases. The meshes of the capillary network in healthy tissues are smaller than the critical layer-thickness of the tissue enclosed, in this way, a certain amount of play is guaranteed (Linzbach, 1955; Opitz et al., 1950).

Capillary-free layers are necessary for the healthy function of tissues. Such layers in parenchymatous organs have a thickness of 10 to 30 μ, in arterial walls they measure about 500 μ; and in cartilaginous tissues, about 1,000 μ. Arterial walls and cartilage are therefore thought to be tissues with slow metabolism (Burger et al, 1927). Researches on metabolism have shown that the respiration of these tissues is from one-tenth to one-twentieth that of parenchymatous tissues (Briggs et al., 1949; Kirk et al., 1954, Schutte, 1956). The greater formation of acid mucopolysaccharides in these tissues can be related to their relatively high glycolysis (Altshuler et al., 1954), and their presence seems to be a gage of the relatively low metabolic rate attributed to them (Linzbach, 1944) Arteries with walls thicker than 500 μ possess vasa vasorum. In contrast with the muscular arteries of the extremities, the wall of the human aorta, thicker than 10^3 μ, is supplied from the adventitia in the external third of the media by vasa vasorum (Ramsey, 1936–1937) Since the blood can flow into the capillary ramifications of the vasa vasorum of the aorta only if their internal pressure is greater than the compressive force on the aortic wall, it is necessary to assume that this condition obtains The internal two-thirds of the aortic wall is nourished by both the blood of the lumen and through the vasa vasorum Since the effective filtration pressure of the aortic endothelium is very low, the transfer of material through it can take place either by diffusion or active forces The filtration forces become effective only in the subendothelial connective tissue, in part radially towards the outside of the wall and in part longitudinally. The conditions obtaining in the aortic endothelium are, therefore, basically different from those in the capillary endothelium. Because of the compressive force inside the aortic wall, the effective filtration pressure at the limiting surfaces of the vasa vasorum must be small, too. As the radial filtration forces of the wall decrease from the inside out, the substances leaving the vasa vasorum can move into the internal wall layers only by diffusion. In the internal layers of the arterial wall, which are free of vessels, the total supply of nutritional substances is not determined, as in parenchymal organs, essentially by filtration, but rather by diffusion or active transferring forces, while filtration is effective only inside the wall layers The internal layers, which are free of vessels, vary in size in various species. In the giraffe, they are more than 1,000 μ in thickness (Goetz et al., 1958), but this is composed of solely elastic tissue and contains no muscle fibers, in contrast to the human aorta.

In the veins and pulmonary artery, the vasa vasorum penetrate down to the intima because, in these vessels, the mean internal pressure (and, therefore, the compression) is smaller than the mean capillary pressure of the vasa vasorum. This different structure is necessary because the supply of blood from the lumens of these vessels is definitely less than that in the arteries.

From this brief review of the normal functional anatomy of the arteries, it appears that the entire arterial system, as well as every part thereof, represents a complicated biological balance that can be altered by different causes

Development of the Arteries. In contrast to other organs and tissues, arterial walls continue to grow throughout life (Rossle et al, 1932). A few arteries grow in proportion to the weight of the heart, e g., the femorals, the coronaries, the aorta, and the pulmonary artery (Linzbach, 1944; Schoenmackers, 1949, Meyer et al., 1956, Hieronymi, 1956). The splenic artery, however, grows more rapidly than the heart, the cerebral arteries in young human beings grow more slowly. In man, corresponding arteries reach the same thickness about 10 years later in females than in males Strong and muscular men have thicker arterial walls than slim persons of the same age. In obese persons, the arteries often have thin, smooth walls (Bähr, 1938; Linzbach, 1944, Selberg, 1951). Certain arteries are most developed in the intima, i e., the aorta and the

is deposited first in the internal then in the external layers of the arteriolar walls Finally there is destruction of the wall structures, which become impregnated with lipoid material The narrowed lumen of the vessel usually has an eccentric position. A relationship between arteriolosclerosis and hypertension has been shown (Smith, 1955, 1956). The mechanism of formation of this deposit is unknown After the age of twenty the central arterioles of the spleen follicles have already been affected, while the small vessels of the trabeculae are spared In advanced age, the arterioles of kidney, pancreas, and myocardium (Wegelin, 1944; Linzbach, 1955) are affected The basal arteries of the brain show only mild changes while the middle cerebral artery and the small branches can be severely affected.

PATHOGENESIS OF ARTERIOSCLEROSIS

During the last 100 years many hypotheses about the pathogenesis of human arteriosclerosis have been proposed, some of which became a "profession of faith."

Thrombus Theory. Rokitansky (1852) explained the thickenings of the intima of the aorta as thrombotic deposits This hypothesis was reasserted in modified form by Duguid (1948) The theory is based on the observation that arterial thrombi of the wall, sometimes in the form of flat deposits of fibrin, are promptly covered by the endothelium and are incorporated in the intima, hyalinized, and organized If the thickness is sufficient, the central areas can slough off and cause the precipitation of fatty material. If arteriosclerosis is already present, *secondary thrombi* are not rare and can have an influence on the ultimate growth of the plaques, especially in the coronary arteries Lubarsch (1905) showed arterial thrombi of the wall in 22 per cent of 425 cases of arteriosclerosis However, it is unlikely that the plaques of the intima are primarily formed by thrombosis The majority of the newly formed plaques of the intima are free of disintegration products of hemoglobin In old plaques, the demonstration of fibrin and hemosiderin is not always evidence of thrombosis since they can also originate from ruptured, newly formed vasa vasorum (Muller, 1919, 1955) under the basal portion of the plaques Fibrin can also penetrate the intima from the blood (Meyer, 1949).

Inflammation Theory. Virchow designated arteriosclerosis as *endarteritis chronica deformans.* It is clear that his conception of inflammation included the degenerative processes. This hypothesis of the inflammatory cause of arteriosclerosis has been subsequently resurrected and confirmed (Klinge, 1933; Bredt, 1941; Holle, 1943; Meyer, 1949). Two different mechanisms are thought to exist.

1. Primary, toxoinfectious, and inflammatory changes of the media (rheumatic fever, infections).

2. Changes in permeability of the endothelium due to infection with resulting penetration of plasma into the intima, especially in rheumatic fever and glomerulonephritis.

The advocates of this theory cannot answer several objections, and it is unlikely that inflammation can be accepted, in general, as the cause of arteriosclerosis.

Hemodynamic Theory. This concept is impaired by the difficulty of explaining why purely physical phenomena should cause an irregular increase in the thickness of arterial walls (Muller-Mohnssen, 1957). The theory of Thoma (1911, 1922, 1923) combines several theories He considers that the primary process of arteriosclerosis is a degeneration of the media followed by dilatation of the vessel and secondary, compensatory proliferation of the intima Gradients of pressure in different directions in the intima would cause a focal proliferation of the intima

The "Wear" Theory. This theory has played an important role in research without offering a definition for "wear." Aschoff (1925, 1939) believed that certain points of the arterial system were exposed to a proportionately greater mechanical load which, in time, would produce local destruction and degeneration of the arterial walls It would be possible, with some limitations, to agree with this theory regarding the early changes in the lamina elastica interna, since these are of great importance in the biological balance of the arterial walls There is no doubt that the internal elastic layers are submitted to severe changes in tension due to changing diameter.

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The Pathogenetic Significance of the Early Changes. Arterial growth and all the aforementioned early changes, with the exception of the lipoid deposits, are not macroscopically striking but have something in common: the tissue of the wall of the arteries is eventually thickened. When the lamina elastica interna is intact, compression of the intima toward the inside is relatively high; toward the outside, low. Conversely, when the membrane is destroyed, the pressure within the intima will decrease while pressure will increase on the outside of the media. The decreasing compression in the intima favors a flow of tissue fluids from the adjacent intimal spaces in the region of minimum pressure, with the ensuing fibroelastic transformation. However, increasing pressure inside the media shifts the critical pressure to the outside until flow can occur in the vasa vasorum, so that some of the vasa vasorum are blocked. The increase of pressure in the media, after local destruction of the lamina elastica interna causes an enlargement of that part of the wall which is not supplied with blood, especially when there is a thickening of the intima.

The early and severe destruction of the internal elastic membrane of the coronary arteries due to considerable proliferation of the intima of these arteries, probably begins during youth and is favored by the flow of tissue fluids from the intima of the aorta The strongly formed lamina elastica interna of the cerebral arteries, on the other hand, guarantees high compression of the intimal space in these vessels. As there is also a thin media, these arteries are affected only at a relatively advanced age (Wolkoff, 1933).

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Fig. 15-3. Scale-like tightened endothelia over an arteriosclerotic calcified plaque of intima of human aorta (woman of 45). The endothelia were loosened from each other by the strong pressure of the cover glass (Ringer; electron microscope, immersion in oil). Examined 21 hr after death.

THE COMPLETE PICTURE OF ARTERIOSCLEROSIS

The typical picture of arteriosclerosis is characterized in the *aorta* and *coronary arteries* by the atheromatous plaques on the intima and relatively little involvement of the media (Marchand, 1904). The localization of the lesions usually corresponds to those points in which the early changes are also most intensive. The typical lesions are plaquelike fibrous thickenings of the intima with deposits of fat and calcium in a necrotic area below the plaques near the media. The tissues underlying the plaques can be supplied by vasa vasorum through the media. Alterations of the endothelium directly related to the formation of the plaques, have not been proved However, calcified plaques of the intima may present a secondary, scaly hardening of the endothelium (Fig. 15-3). The postmortem dissolution of hardened endothelium proceeds more slowly than that of normal tissue. The formation of giant cells can also be shown in nonarteriosclerotic areas on the endothelium of the aorta (Linzbach, 1952, Linzbach et al, 1957).

In the *muscular arteries*, especially those of the legs, it is possible to demonstrate primary foci of degeneration of the internal third of the media with secondary calcification in the form of plaques (*trachea-like arteries,* Monckeberg, 1903, 1904). In obliterating arteriosclerosis of the legs, the plaques of the intima, together with thrombosis, are important while calcification of the intima is less marked (Allen et al, 1955).

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The "Wear" Theory. This theory has played an important role in research without offering a definition for "wear" Aschoff (1925, 1939) believed that certain points of the arterial system were

terial walls It would be possible, with some limitations, to agree with this theory regarding the early changes in the lamina elastica interna, since these are of great importance in the biological balance of the arterial walls. There is no doubt that the internal elastic layers are submitted to severe changes in tension due to changing diameter.

Aging Theory. A real predisposition to arteriosclerosis due to senility was mathematically proved by Schinz et al. (1955). Burger (1939) advocated this theory and considered the increasing deposition of calcium, choleste-

rol, and mucopolysaccharides in the arterial wall, and the loss of water followed by decreased diffusion to be the causes. Daily experience casts doubt about the influence of the age factor on the development of arteriosclerosis As stated by Katz (1952), this theory is patently wrong.

Lipid Theory. This theory states that the content and type of fats in the plasma are the primary and essential causes for the formation of fibrous, fatty thickenings of the intima. The focal character of the changes presupposes additional factors causing localization in certain areas The fundamental experiments were performed at the beginning of this century by Ignatowski (1909), Chalatow (1912), and Anitschkow (1913, 1914, 1922, 1933), who produced arteriosclerosis in rabbits, chickens, and, under particular experimental conditions in other animals, through the use of a diet rich in cholesterol Fatty foci were produced in the thoracic aorta, bearing a striking similarity to the lipoid spots in the human aorta. If the diet is continued for a long time, the foci, containing proliferating cells that phagocyte fat (Duff et al., 1957), undergo degenerative changes and connective tissue proliferation (Scarff, 1927, Anitschkow, 1933) If mechanical, thermal, or chemical lesions are produced in the wall during the experiment, the lipid foci localize chiefly in the damaged areas. If, however, an experimental focal calcification of the media is produced first, through injection of epinephrine or vitamin D, the intimal foci form only at the points of calcification These experiments show that local lesions, causing a loosening and expansion of the arterial wall, favor the deposition of fatty materials in the intima. Conversely, changes which reduce the extensibility of the vascular wall, e.g , calcification of the media, hinder local deposition of fat in the intima This can be explained by the fact that calcification of the media guarantees a relatively high compression of the intima and increases its resistance In the same way, severe calcification of the media (Monckeberg type) is usually accompanied by relatively rare formation of plaques on the intima while arteriosclerosis obliterans of the femoral arteries is usually accompanied by rare calcification of the media Even though the connective tissue is able to synthesize cholesterol, it seems to be proved that the fatty material deposited in the intima comes from the blood. Several experiments lead to the belief that the high-molecular-weight lipoproteins can migrate into the intima through the endothelium in an unknown way (Evans et al , 1957; Goldberg et al., 1957). The experiments of Hueper (1941, 1956) have shown that other substances of high molecular weight (polyvinyl derivatives) can migrate from the blood into the intima. The most difficult and until now unsolved problem of the lipid theory is the question whether results of experiments on animals are valid when applied to human beings. The production of experimental arteriosclerosis requires relatively large amounts of cholesterol, equivalent to a daily supply of cholesterol about twenty times the normal values, if applied to man. Keys (1952), therefore, says: "From the animal experiments alone, the most reasonable conclusion would be that the cholesterol content of human diet is unimportant in human atherosclerosis." The atheromatosis caused by overload feeding differs from human atherosclerosis, apart from the heterogenous localization of the foci, because, not only are the arteries affected but lipoid deposits occur in the muscles, liver, spleen, kidneys, lungs, and eyes (Buck, 1954, Evans et al., 1957). Support for the utilization of the lipid hypothesis in human arteriosclerosis is given by the positive correlation of increased serum cholesterol content and atherosclerosis in diabetes, hypothyroidism, and idiopathic hypercholesterolemia However, it might be that entirely different factors play a role in these diseases. In diabetes, one should consider the importance of hypertension and acidosis; in hypothyroidism, that of disturbances of the metabolism and tissue respiration. Besides, it is necessary to keep in mind that long-lasting lipid nephrosis with high cholesterol values in the blood may occur without concomitant atherosclerosis. It is difficult to understand why human arteries usually are spared until the fourth decade of life in spite of the fact that human cholesterolemia is usually three times higher than that of rabbits (Duff et al, 1951) Biochemical studies on the composition of hematic fat, i e , increase of cholesterol/phospholipid ratio, decrease of alpha lipoproteins, and increase of beta lipoproteins (Bazz et al , 1951), demonstration of large molecules of the so-called S_f 10 to 20 lipoproteins

(Gofman et al., 1950, 1952) did not give clear-cut results in human beings One of the difficulties is due to the fact that it is impossible during life to evaluate with certainty the extent and severity of arteriosclerosis. At present, studies made during life to determine the *biochemical atherogenic index* failed to show any correlation with autopsy data (Paterson, 1954; Chapman et al, 1956) Comparative geographic and sociological studies can supply valuable data in regard to the importance of dietary factors in the causation of arteriosclerosis. However, they presuppose an exact quantitative and qualitative evaluation of arteriosclerosis on the autopsy material The work of Gore and Tejada (1957) reveals the trends which prevail in this field

Theory of Insufficient Nutrition of the Arterial Wall. This theory is based on the concept that both the (diffuse and the focal) processes of growth and the degenerative early changes lead to an irregular thickening of those sections of the arterial wall which are deprived of blood supply Since the thickness of the arterial walls increases steadily throughout life, the sections not receiving sufficient blood finally exceed the critical thickness This produces, at certain points, insufficient nutrition, followed by focal necrosis at the center of the thickened layers

In those arteries which present a predominant growth of the intima (aorta, coronary arteries) the foci of necrosis with deposition of fatty material and calcium salts are mainly situated in the deep layers of the plaques, near the media On the other hand, in those arteries which present a predominant growth of the media (femoral, renal) the centers of the degenerative processes are situated chiefly in the media, together with secondary fibrosis or dystrophic calcification It is not known whether the insufficient nutrition of the arterial wall is due to the fact that critical thickness is reached, resulting in deprivation of oxygen or nutrients (i.e., glucose), or to imperfect drainage of toxic metabolites. Actual measurements have proved that the critical thickness of the femoral artery is reached when the area of this vessel is about 12 mm² (Linzbach, 1944), that of the aorta when it attains a weight over 70 Gm (Meyer, 1951). The linear critical layer-thickness is estimated by Geiringer (1951) for the coronary arteries as 350 μ and for the aorta as 500 μ Considering the natural variations, it is possible to say that, below the critical layer-thickness, the arterial changes are essentially early ones while, above it the whole picture of arteriosclerotic foci with local tissue necrosis appears.

The local tissue necrosis that characterizes well-developed arteriosclerotic foci produces organizing processes which lead to secondary vascularization of the media and of the deep layers of the intima from the vasa vasorum (Linzbach, 1944, Geiringer, 1951; Drury, 1954). The organizing vessels evidently carry blood, because hemorrhages may occur in the depths of the intimal plaques. From this it appears that the compression in the deep layers of the intima must be lower than that in the newly formed vessels. This low compression can only be due to the fact that the internal connective layers of the arteriosclerotic plaques can absorb a large part of the wall tension The relationship between compression inside the plaques and that of neighboring spaces is significant in the further increase in the size of the focus. Not only is there a decrease of pressure in the intima, which favors an inflow of tissue fluids, but, through the presence of products of necrosis, the osmotic pressure of the foci can increase, thus attracting fluid from the surrounding tissues and the blood Whether the fatty substances present in the plaques result from tissue destruction, are synthetized, or originate from the blood and accumulate at the points of minimum pressure, is a still unsolved question In the last case, the lipid content of the blood would determine to a certain extent the fat content of the arteriosclerotic plaques, but would not be its cause. On the other hand, the uncommon and rapid fatty degeneration and the subsequent destruction of cells in a neglected tissue culture shows that tissue hypoxia may account for a large proportion of the visible fatty substances.

The hypothesis of faulty nutrition of the arterial wall explains the tendency toward arteriosclerosis of *muscular* men and hypertensive persons. Experiments have shown that the thickness of arterial walls increases more rapidly in men than in women, in athletes than in weaklings, and in hypertensive than in normotensive or hypotensive persons Therefore, the critical layer-thickness is reached

earlier in the former. Since the veins and the pulmonary artery are supplied with abundant vasa vasorum and are subjected to low compression, these vessels almost never reach the critical thickness. This is why sclerotic changes occur more seldom, or only to a small extent, in these vessels.

CONCLUSION

This review has discussed the unexplained pathogenesis of arteriosclerosis. The severe drop in pressure which occurs in the arterioles justifies the theory that the centrifuged stream of fluid in the intimal spaces of these vessels is relatively greater than it is in all the other vascular areas. This is particularly true when the flow from within to without the wall is opposed by high tonus of the muscular fiber, as in hypertension. In this particular case, there would be the condition for a "stasis" of fluids in the sense of Hueck (1920).

Considering the anatomical structure, the physical behavior of the pressure inside arterial walls, and their peculiar conditions of nutrition, a pathogenetic theory of arteriosclerosis has been developed. This permits the unification of the various earlier hypotheses

The new concept states that those sections of arterial wall which have no vessels and receive poor nourishment enlarge (1) due to a process of thickening, the speed of which depends upon age, constitution, sex, type of arteries, blood pressure, and local dynamic factors; and (2) because of all the known pathological early changes. These early changes produce a definite tendency to local changes

Growth and early changes cause the wall to reach a critical layer-thickness at a certain point; after this, local disturbances of nutrition arise and cause the development of arteriosclerotic foci with phenomena of destruction and organization.

In the arteries in which increases of the wall thickness occur, particularly in the intima (e g , aorta, coronary arteries), arteriosclerotic changes of the intima are most frequent, in those arteries in which the increase occurs particularly in the media (e.g , femoral and renal arteries), the changes occur chiefly in that tissue layer.

2

Gross and microscopic changes caused by atherosclerosis and arteriosclerosis

CHARLES BRUCE TAYLOR

The term *arteriosclerosis* is usually employed as a general term covering many of the arteriopathies However, it is only a descriptive term meaning "hardening of the arteries" and wisely has been excluded from the classification of arteriopathies by the Committee on Nomenclature of The American Society for the Study of Arteriosclerosis (Wolffe et al). Since arteriosclerosis only implies that an artery is hard, due to scarring and calcification, and does not indicate pathogenesis, this term might best be relegated for use as a descriptive adjective for end-stage changes in arteries due to a variety of causes The afore-mentioned classification by the Committee on Nomenclature will be followed in this section. *Atherosclerosis* will be considered extensively, other arteriopathies will either be discussed only briefly or merely defined

Classification of Arteriopathies Based on Report of Committee on Nomenclature of American Society for Study of Arteriosclerosis

- I Degenerative arteriopathies
  - A. Atherosclerosis
  - B. Medial calcific sclerosis (Monckeberg's)
  - C Arterionecrosis
- II Productive or hyperplastic arteriopathy (hypertensive vascular disease)
- III. Inflammatory arteriopathies
  - A Infectious
    - 1 Bacterial
    - 2. Plasmodial
    - 3. Viral
  - B Attributable to abnormal tissue responses (hypersensitivity)
    - 1. Polyarteritis nodosa (periarteritis nodosa, essential panarteritis)
    - 2 Arteritis associated with systemic lupus erythematosus
    - 3 Arteritis associated with scleroderma and acrosclerosis
    - 4. Arteritis associated with rheumatic fever
    - 5 Thromboangiitis obliterans
    - 6 Cranial arteritis (giant-cell arteritis; temporal arteritis)
  - C. Traumatic arteritis
    - 1. Chemical arteritis
    - 2 Physical arteritis
    - 3 Mechanical arteritis
  - D. Arteriopathies of undetermined or uncertain origin
    - 1. Thrombotic thrombocytopenic purpura
    - 2. Nodular vasculitis
    - 3. Aortic arch arteritis
- IV. Primary thromboembolic arteriopathies
  - A. Embolism
    - 1. Detached thrombus or vegetation



Fig. 15-4. A. *Early atherosclerotic lesion showing fat-laden macrophages lying in subendothelium and within the confines of the internal elastic lamina. The macrophages are intermingled with fibrocytes which also appear to have proliferated as a response to the increased concentration of lipids in the subendothelial zone B Severe coronary atherosclerosis with intramural hemorrhage and thrombosis The media consists of the darker, more cellular, thin rim of tissue lying just inside the loose-textured adventitia The intima has thickened to three to five times the thickness of the media and consists of grumous plaques lying deep in the thickened intima (lower left), new groups of fat-laden macrophages lying just to the right of the thrombus in the lumen, and dense hyaline scars containing only a few cells and frequent cholesterol clefts Two vasa vasorum are present on the left at the junction of the media with the thickened intima. The dark crescent-shaped area in the thickened intima which lies toward the bottom and the left is a large intramural hemorrhage resulting from rupture of vasa vasorum which had proliferated into a partially degenerated atheromatous deposit. The dark blood clot in the lumen is attached at the site of maximal disruption and inflammation of the endothelium which was caused by the reaction to the intramural hemorrhage In some instances intramural hemorrhage alone may occlude the lumens of coronary arteries, the space occupied by the hemorrhage into the wall being sufficient to completely occlude the lumen.*

2. Air
3. Fat
4. Foreign bodies

B. Essential arteriothrombosis (in situ)

V. Combined forms of arteriopathies

Combination of any of the afore-mentioned arteriopathies. The combination of atherosclerosis and medial calcific sclerosis or arterionecrosis is frequent, and suggests that medial lesions may often determine the localization of atheromas in susceptible individuals

DEGENERATIVE ARTERIOPATHIES

Atherosclerosis. Atherosclerosis has been described as the keystone in the arch of cardiovascular disease and is unquestionably the most important single disease afflicting man today (Katz and Dauber, 1945). Fortunately, the "senescence theory" of the pathogenesis of atherosclerosis is rapidly being replaced by a concerted research effort by scientists who have refused to believe that atherosclerosis is the inevitable result of the physiological aging process. During the past several decades, particularly during the years since World War II, many aspects of this disease have been clarified and it is highly probable that within the next few decades atherosclerosis will become a disease of minor importance.

Atherosclerosis is characterized by intimal deposits of lipids with variable degrees of scarring, hemorrhage, and calcification (Fig 15-4). The genesis of this disease process can be presented better after a brief consideration of the *anatomy and physiology* of arterial tissue Arterial walls have three layers: intima, media, and adventitia. The *intima*, in young, healthy arteries, consists of a layer of endothelial cells and a very thin subendothelial layer. In the thin subendothelial layer there are a few primitive mesenchymal cells with multipotent regenerative powers which play a major role in the repair of vascular tissue and in the genesis of atherosclerosis The *media*, in most arteries, is delineated by an internal and an external

elastic membrane and is composed of variable numbers of additional well-oriented elastic membranes, collagen, and smooth muscle cells lying in a ground substance. The *adventitia* consists of loose connective tissue with its collagenous and elastic fibers running predominantly parallel to the longitudinal axis. *Muscular arteries* have only internal and external elastic membranes, cerebral arteries have only *a thick* internal elastic membrane. Nutrition is supplied to the adventitia and much of the media by *vasa vasorum*. However, the intima and inner media depend upon diffusion from luminal blood for nutrition. This diffusion of luminal plasma into and out of the intima and superficial media appears important in the genesis of atherosclerosis. Indeed, there is considerable clinical and experimental evidence which indicates that plasma lipids precipitate out in the subendothelial spaces of the intima during diffusion to and from the intima and superficial media. Recent studies on monkeys indicate *a critical level* of total serum cholesterol of about 250 mg/100 ml, when levels are 250 mg/100 ml or higher, lipids precipitate in the subendothelium and are phagocytized by the multipotent mesenchymal cells in the subendothelium (Taylor et al., 1957). Phagocytosis of lipids in the subendothelium represents an early form of atherosclerosis (Fig. 15-4A). The propensity of lipids to accumulate within the intima is striking and it would appear that the internal elastic membrane usually *delimits early* deposits of lipids and atheromas in the walls of arteries. Flow of interstitial fluids in the media via vasa vasorum must be accomplished under much more stable conditions because lipids do not precipitate out in this layer unless the structure of the media has been markedly altered. Leary proposed that the presence of lipids in the intima also stimulates proliferation and differentiation of multipotent mesenchymal cells into fibrocytes, resulting in a mixed intimal lesion composed of lipophages and connective tissue (Fig. 15-4). Fibrous elastic scars become quite thick and often form a white pearly *scar over* a foam-cell atheroma; the atheroma later degenerates and leaves a yellow grumous mass of lipids deep *in the thickened* intima (Fig. 15-4B). With the increased thickness of the intima, this portion of the vessel now becomes vascularized with vasa vasorum originating in



Fig. 15-5. Large aneurysms of lower abdominal aorta and left common iliac artery. The site of rupture of the aortic aneurysm lies in the anterior midline in the upper half of the aneurysm. There is marked *ectasia* of the right common iliac and the lesser iliac arteries

the media and from the endothelial surface. These vasa vasorum lie in the poorly formed, often degenerating atherosclerotic plaques and frequently *rupture* with *subsequent hemorrhage* into the plaque (Paterson, 1955). These hemorrhages result in enlargement of atheromas, *greater narrowing* of lumens of vessels and, *all too frequently*, in *occlusion, thrombosis, or both* (Fig. 15-4B). Other late changes consist of severe medial degenerative changes with calcification beneath the atheromas, this *may lead to the development* of aneurysmal *dilatation* and *rupture* (Fig. 15-5). Also, the intimal scars over atheromas may *ulcerate* and lead to *thrombosis*.

Atherosclerosis *may* develop secondary to arteriopathies from other causes (Fig. 15-6) (Waters and Taylor). The unique response of arterial tissue to injury associated with various *arteriopathies* will be reviewed and its

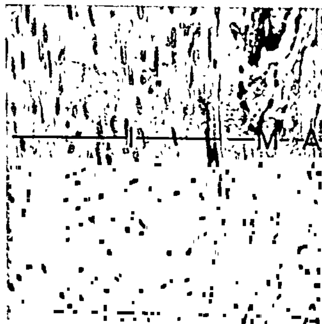


Fig. 15-6. The profound effect of hypercholesterolemia on vascular repair at sites of injury and degeneration is demonstrated *Upper:* Cross section of a healed arterial lesion produced by freezing the aorta of a normocholesterolemic rabbit ingesting a low-fat, cholesterol-free diet. The adventitia (*A*) is composed of dense bundles of collagen The damaged, degenerated media (*M*) has few viable cells and is partially calcified. There is essentially no reparative response in the media. Within the intima (*I*) multipotent mesenchymal cells have proliferated, differentiated, and formed an essentially new arterial wall which lies within the degenerated shell of the old injured media (*M*). *Lower.* Cross section of the inadequate healing process occurring at a site of injury produced by freezing the aorta of a hypercholesterolemic rabbit (average serum cholesterol level, 1,090 mg/100 ml). The adventitia (*A*), degenerated media (*M*), and proliferated intima (*I*) are indicated. Comparison with section above demonstrates the marked alteration in the intimal repair. Lipophages occupy the inner one-half of the proliferated intima The upper half of the intimal scar shows only a few scattered fibroblasts lying in partially hyalinized scar tissue which in some areas shows "mucinous" degeneration.

role in the development of atherosclerosis will be outlined Almost all of the regenerative and reparative capacity of arterial tissue stems from the subendothelial primitive mesenchymal cells mentioned earlier. In the experimental animal, these multipotential cells have the ability to form an essentially new vascular wall in the framework of a proliferated intima (Taylor, 1955). There is very little regeneration of vascular tissue in an injured media In hypercholesterolemic animals and apparently in man, intimal proliferation following medial degeneration consists of a mixed response, with some primitive mesenchymal cells being diverted to phagocytosis of subendothelial lipids, and the more desirable response of regeneration of new functional vascular tissue is adversely affected (Fig. 15-6). Thus, it appears that, *in the moderately hypercholesterolemic man, arteriopathies due to other causes enhance the rate of development of atherosclerosis and jeopardize the vascular repair process* Intimal scars should contain well-oriented new elastic membranes, fibrocytes, smooth muscle cells, and a modest number of well-oriented collagen bundles. In man and in hypercholesterolemic animals, intimal scars are composed of an abundance of fat-laden macrophages, poorly formed, often hyalinized collagen with very meager amounts of poorly oriented elastic tissue; no smooth muscle cells, and a few scattered fibrocytes (Fig. 15-6). With partial loss of elastic and contractile characteristics, the arterial bed is left with a decreased quantity of functional tissue available to dilate and contract with each cardiac cycle. Consequently the potential for development of new arterial lesions, with subsequent development of more atherosclerosis and poor intimal scars, is further enhanced. This vicious cycle of events explains, in part, why atherosclerosis usually develops more rapidly during the later decades of life.

As mentioned previously, atherosclerosis is initially confined to the intima. However, if disruptions occur in the internal elastic membrane, *many lipid-laden macrophages are found in the media.* A common place for such a change is in larger cerebral arteries at the base of the brain where the so-called "collar-button" atheromatous lesion is found, a large intimal atheroma becomes constricted as it passes through a defect in the internal elastic membrane then enlarges again in the media

The distribution of atherosclerosis is interesting The disease is uncommon in the lesser pulmonary circulation unless pulmonary arterial hypertension is present. In the systemic circulation, the disease affects the aorta and many of its primary and secondary branches, hypertension hastens the genesis of atherosclerosis in these vessels. Almost all large and moderate-sized arteries of the systemic arterial

tree lying in loose-textured tissue may be sites of atherosclerosis However, when these vessels enter firm parenchymatous organs or tissues, atherosclerosis no longer is present. A striking example of this is the severe atherosclerosis which is present in epicardial coronary arteries and renal arteries before they enter the myocardium or renal parenchyma Immediately after entrance into their respective organs, atherosclerosis ceases. Arteries within firm parenchymatous tissue may show marked intimal scarring but almost never show atheromatosis.

Prevention of Atherosclerosis. There is a good deal of clinical and experimental evidence which indicates that atherosclerosis is a disease that could be largely eradicated by preventive medical measures. There is indirect evidence in studies of population groups by Keys and Anderson (1955), substantiated by studies of monkeys (Taylor et al, 1957), which indicates that atherosclerosis develops only when serum cholesterol levels are above 250 mg/100 ml, conversely, if levels are below about 200 mg/100 ml, atherosclerosis will not develop even in the presence of arterial injury Fortunately, the medical profession and populations in overfed nations are slowly but surely adopting the philosophy that cholesterol and other fats should be reduced to about 20 to 30 per cent of the current average rate of consumption With reduced levels of total serum cholesterol, the precipitation and accumulation of lipids in the intima of arteries should be reduced to such an extent as to markedly inhibit the development of atherosclerosis and thus make it a disease of minor importance

Reversibility of Atherosclerosis. The reversibility of atherosclerosis deserves careful consideration because of the prevailing concept that atherosclerosis is not reversible. Reversibility of the disease was demonstrated in experimental animals many years ago (Anitschkow, 1933) Evidence for reversibility of the disease in human beings is necessarily indirect but most pathologists feel the disease undergoes regressive changes in relatively short periods in patients with terminal carcinoma, tuberculosis, and other wasting diseases There is a modest amount of material in the literature comparing atherosclerosis in wasting diseases with the affection in patients dying suddenly (Wilens, 1947) It is important to keep in mind that atherosclerosis consists of foreign material (lipids) lying in cells and interstitial spaces in arterial tissue and that, under proper conditions, these lipids can be removed from the tissue. Proper conditions would appear to be *a reduction in the total concentration of certain plasma lipids* (with the total serum cholesterol serving as an index of their concentration), so that lipids can be mobilized and removed from the arterial wall. As originally shown by Anitschkow in experimental animals, reversal of the disease requires relatively long periods of time; in the experimental animal, florid atherosclerotic lesions are almost completely replaced by an intimal scar within periods of 18 to 24 *months*.

MEDIAL CALCIFIC SCLEROSIS (MÖNCKEBERG'S)

Monckeberg's medial calcific sclerosis is a disease of uncertain etiology which is characterized by medial calcification and fibrosis The intima may show only fibrosis or may show concomitant atherosclerosis. Muscular arteries, such as the femoral, tibial, and radial, are affected It is a disease of adult life which tends to progress with aging. Femoral arteries show segmental calcification in circumferential rings resembling cartilaginous rings in the trachea. Smaller arteries such as the radials show extensive pipestem medial calcification. Hueper, 1944, has attributed the disease to calcification following a degenerative change due to toxic vasotonic agents of either exogenous or endogenous origin and cites a number of known exogenous agents that have resulted in medial calcification experimentally, these toxic agents include epinephrine, vitamin D, and nicotine.

ARTERIONECROSIS

Cystic Medionecrosis. Erdheim (1930) described the formation of mucoid cysts in areas of dissolution of elastic tissue and smooth muscle cells and called the condition "medionecrosis aortae idiopathica cystica" It has been shortened to *cystic medionecrosis* and is generally accepted as the predisposing lesion in the majority of dissecting aneurysms of the aorta Hypertension is a common predisposing clinical condition. It has been suggested that the degenerative medial lesions may be either secondary to obliterative changes in the vasa

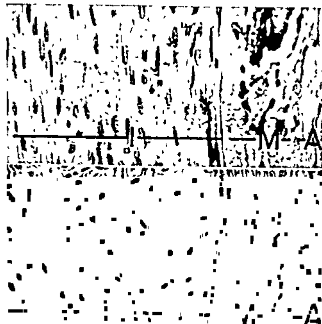


Fig. 15-6. The profound effect of hypercholesterolemia on vascular repair at sites of injury and degeneration is demonstrated. *Upper:* Cross section of a healed arterial lesion produced by freezing the aorta of a normocholesterolemic rabbit ingesting a low-fat, cholesterol-free diet. The adventitia (A) is composed of dense bundles of collagen. The damaged, degenerated media (M) has few viable cells and is partially calcified. There is essentially no reparative response in the media. Within the intima (I) multipotent mesenchymal cells have proliferated, differentiated, and formed an essentially new arterial wall which lies within the degenerated shell of the old injured media (M). *Lower:* Cross section of the inadequate healing process occurring at a site of injury produced by freezing the aorta of a hypercholesterolemic rabbit (average serum cholesterol level, 1,090 mg/100 ml). The adventitia (A), degenerated media (M), and proliferated intima (I) are indicated. Comparison with section above demonstrates the marked alteration in the intimal repair Lipophages occupy the inner one-half of the proliferated intima. The upper half of the intimal scar shows only a few scattered fibroblasts lying in partially hyalinized scar tissue which in some areas shows "mucinous" degeneration.

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grees of arterial necrosis and inflammation and usually an associated thrombosis proximal and distal to the embolic occlusion

Essential Arteriothrombosis (in situ). In conditions associated with hypercoagulability of blood, such as *polycythemia vera*, thrombosis occurs in smaller arteries without apparent local vascular changes which would account for the thrombosis

COMBINED FORMS OF ARTERIOPATHIES

Any of the afore-mentioned arteriopathies may be superimposed one upon the other As discussed above, atherosclerosis frequently develops at sites of repair of arterial tissue, regardless of the pathogenesis of the injury or degeneration. Since atherosclerosis is such an important disease, the fact that its rate of development in man is increased by the presence of other arteriopathies deserves reiteration. However, it is much more important that the preventability of atherosclerosis in both normal arterial tissue and the loci of other arteriopathies be stressed Recent observations on monkeys (Taylor et al, 1957) demonstrate a critical range (about 250 mg/100 ml) of serum cholesterol above which lipids accumulate in arterial tissue When levels of serum cholesterol are below 200 mg/100 ml, lipids do not accumulate in either normal arterial tissue or at sites of artificially produced arteriopathy. Work by earlier workers reviewed by Keys and Anderson (1955), and their more recent studies, although of necessity not as clear-cut as the studies on monkeys, indicate a very similar picture in man.

VASCULAR DISEASE IN DIABETES

This special form of degenerative vascular disease was not included in the classification of arteriopathies which was followed in this section. However, the author feels that vascular disease in diabetes mellitus is an important and separate disease entity and should be mentioned at least briefly. A more complete discussion is available in a publication by Warren and LeCompte (1952). In diabetes mellitus, medial degenerative changes are conspicuous in small arteries, arterioles, venules, and capillaries. It has been suggested by Dry and Hines (1941) that diabetes mellitus is an inherent weakness affecting both carbohydrate metabolism and certain poorly understood factors concerned in the maintenance of normal, healthy arterial walls They further suggest that medial degenerative changes in vasa vasorum may result in medial degeneration of larger arteries just as medial degeneration of vasa nervorum and retinal arterioles result in diabetic neuropathies and diabetic retinitis, respectively. Thus, many of the late arterial lesions of diabetes mellitus would be examples of combined arteriopathies: degenerative changes, primarily medial, associated with diabetes mellitus with superimposed atherosclerosis overlying sites of medial degeneration.

vasorum or to the direct effects of hypertension on medial structures. However, the cause of this disease is uncertain.

Toxic Arterionecrosis. This lesion is characterized by necrosis and degeneration in various parts of all coats of the arteries and is ascribed to either exogenous (e.g., diphtheria) or endogenous (e g., renal, adrenal) toxins.

Arterionecrosis of Physical Origin. This is necrosis of arterial tissue due to physical agents such as gross mechanical or thermal trauma.

Arteriolar Necrosis (Arteriolonecrosis). The pathological anatomy of this lesion consists of intramural fibrinoid necrosis with variable degrees of deposition of perivascular fibrinoid, focal hemorrhagic and intravascular thrombosis. The most severe changes are seen in the renal afferent arterioles and less frequently in the renal intralobular arteries and other arterioles. These lesions are characteristic of so-called "malignant" or "accelerated" hypertension and are superimposed on hyperplastic arteriopathy.

PRODUCTIVE OR HYPERPLASTIC ARTERIOPATHY (HYPERTENSIVE VASCULAR DISEASE)

Protracted increased pressures in the systemic or pulmonary arterial system result in hyperplastic changes, primarily in small arteries and arterioles Arteries develop muscular hyperplasia and intimal thickening with formation of new elastic lamina, later, medial fibrosis develops Arterioles show muscular hyperplasia with subsequent hyaline medial degeneration.

INFLAMMATORY ARTERIOPATHIES

Infectious. SYPHILITIC ARTERIOPATHY This is due to the *Treponema pallidum* The adventitia and vasa vasorum are primarily affected, other changes are secondary

BACTERIAL. Local invasion of bacteria, particularly pathogenic *cocci*, causes this arteriopathy which can develop into a so-called mycotic aneurysm.

PLASMODIAL. This is a disease of small arteries associated with the agglutination of erythrocytes in malaria.

VIRAL Rickettsial as well as viral infections affecting small arteries are included in this category.

Attributable to Abnormal Tissue Responses (Hypersensitivity). This group of arteriopathies has been listed above and will be only briefly mentioned here. The cause of each disease is not clearly established but, in many instances, a hypersensitive reaction is strongly implicated.

Traumatic Arteritis. CHEMICAL. Chemical agents including drugs may injure vessels by local contact at sites of injection or be indirectly injurious following absorption

PHYSICAL. Physical agents that may cause arterial injury and arteritis include light, heat, cold, x-rays, and radioactive substances.

MECHANICAL. Mechanical forces may injure arterial tissue by direct impact or indirectly by applying abnormal forces to the body generally; e.g., rapid deceleration in an automobile accident may result in an injury to or tear of the aortic arch (Tannenbaum and Ferguson, 1948).

Undetermined or Uncertain Origin. In this category are arteriopathies of most uncertain origin. In certain other arteriopathies categorized earlier, the pathogenesis was not clearly established but etiologic factors were felt to be sufficiently established to warrant their classification elsewhere.

THROMBOTIC THROMBOCYTOPENIC PURPURA This disease is relatively uncommon and, according to Meacham et al. (1951), has its primary lesion in arterioles and capillaries Focal intimal lesions develop, followed by platelet thrombi and a secondary thrombocytopenia with purpura.

NODULAR VASCULITIS. This disease is one of several affecting subcutaneous adipose tissue and its vessels. This group of diseases has been described by Allen (1957).

AORTIC ARCH ARTERITIS This disease has been variously labeled as *pulseless disease*, young female arteritis, and aortic arch arteritis It is a proliferative arteritis involving the aortic arch and its major branches Ross and McKusick (1953) have reviewed 100 cases of this syndrome

PRIMARY THROMBOEMBOLIC ARTERIOPATHIES

Embolism. Arterial reactions associated with lodgement of emboli from thrombi, vegetations, and such foreign substances as air, fat, and other materials, consist of variable de-

grees of arterial necrosis and inflammation and usually an associated thrombosis proximal and distal to the embolic occlusion.

Essential Arteriothrombosis (in situ). In conditions associated with hypercoagulability of blood, such as *polycythemia vera*, thrombosis occurs in smaller arteries without apparent local vascular changes which would account for the thrombosis.

COMBINED FORMS OF ARTERIOPATHIES

Any of the afore-mentioned arteriopathies may be superimposed one upon the other. As discussed above, atherosclerosis frequently develops at sites of repair of arterial tissue, regardless of the pathogenesis of the injury or degeneration. Since atherosclerosis is such an important disease, the fact that its rate of development in man is increased by the presence of other arteriopathies deserves reiteration. However, it is much more important that the preventability of atherosclerosis in both normal arterial tissue and the loci of other arteriopathies be stressed. Recent observations on monkeys (Taylor et al., 1957) demonstrate a critical range (about 250 mg/100 ml) of serum cholesterol above which lipids accumulate in arterial tissue. When levels of serum cholesterol are below 200 mg/100 ml, lipids do not accumulate in either normal arterial tissue or at sites of artificially produced arteriopathy. Work by earlier workers reviewed by Keys and Anderson (1955), and their more recent studies, although of necessity not as clear-cut as the studies on monkeys, indicate a very similar picture in man.

VASCULAR DISEASE IN DIABETES

This special form of degenerative vascular disease was not included in the classification of arteriopathies which was followed in this section. However, the author feels that vascular disease in diabetes mellitus is an important and separate disease entity and should be mentioned at least briefly. A more complete discussion is available in a publication by Warren and LeCompte (1952). In diabetes mellitus, medial degenerative changes are conspicuous in small arteries, arterioles, venules, and capillaries. It has been suggested by Dry and Hines (1941) that diabetes mellitus is an *inherent weakness* affecting both carbohydrate metabolism and certain poorly understood factors concerned in the maintenance of normal, healthy arterial walls. They further suggest that medial degenerative changes in vasa vasorum may result in medial degeneration of larger arteries just as medial degeneration of vasa nervorum and retinal arterioles result in diabetic neuropathies and diabetic retinitis, respectively. Thus, many of the late arterial lesions of diabetes mellitus would be examples of combined arteriopathies: degenerative changes, primarily medial, associated with diabetes mellitus with superimposed atherosclerosis overlying sites of medial degeneration.

vasorum or to the direct effects of hypertension on medial structures. However, the cause of this disease is uncertain.

Toxic Arterionecrosis. This lesion is characterized by necrosis and degeneration in various parts of all coats of the arteries and is ascribed to either exogenous (e.g., diphtheria) or endogenous (e.g., renal, adrenal) toxins.

Arterionecrosis of Physical Origin. This is necrosis of arterial tissue due to physical agents such as gross mechanical or thermal trauma.

Arteriolar Necrosis (Arteriolonecrosis). The pathological anatomy of this lesion consists of intramural fibrinoid necrosis with variable degrees of deposition of perivascular fibrinoid, focal hemorrhagic and intravascular thrombosis The most severe changes are seen in the renal afferent arterioles and less frequently in the renal intralobular arteries and other arterioles These lesions are characteristic of so-called "malignant" or "accelerated" hypertension and are superimposed on hyperplastic arteriopathy.

PRODUCTIVE OR HYPERPLASTIC ARTERIOPATHY (HYPERTENSIVE VASCULAR DISEASE)

Protracted increased pressures in the systemic or pulmonary arterial system result in hyperplastic changes, primarily in small arteries and arterioles Arteries develop muscular hyperplasia and intimal thickening with formation of new elastic lamina, later, medial fibrosis develops Arterioles show muscular hyperplasia with subsequent hyaline medial degeneration.

INFLAMMATORY ARTERIOPATHIES

Infectious. SYPHILITIC ARTERIOPATHY This is due to the *Treponema pallidum* The adventitia and vasa vasorum are primarily affected, other changes are secondary

BACTERIAL. Local invasion of bacteria, particularly pathogenic *cocci*, causes this arteriopathy which can develop into a so-called mycotic aneurysm.

PLASMODIAL This is a disease of small arteries associated with the agglutination of erythrocytes in malaria

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[illegible]

head et al, [illegible]). [illegible] either by the injection of sulfonamides or by surgery, a peculiar type of medial calcification follows, this has been attributed to the development of hyperparathyroidism secondary to the kidney insufficiency. All these experiments point to the fact that a normally functioning kidney is necessary for the maintenance of the integrity of the medial layer of the arteries

Dietary Factors. The influence of diet in the maintenance of normal arteries has been demonstrated mainly under the following circumstances.

CHOLINE DEFICIENCY. This deficiency in rats produces medial sclerosis of the aorta and the coronary arteries which is aggravated by cholesterol feeding

LATHYRISM Rats and turkeys fed with seeds of *Lathyrus odorata* develop dissecting aneurysms of the aorta and bone lesions.

VITAMIN E DEFICIENCY. This deficiency in guinea pigs, but not in rats, produces medial degeneration and calcification of the aorta

ENDOCRINE GLANDS Rats with diabetes caused either by alloxan administration or by subtotal pancreatectomy show arteriolar hyalinization, it is possible that these changes are dependent not on the pancreas but on a secondary kidney damage.

OTHER FACTORS The intravenous injection of al- [illegible] necrosis of the [illegible] infiltration is observed and a lesion similar to human atherosclerosis may result

From the above results it appears that, although an injury to the arterial media can be produced in many ways, the histological picture may show a great uniformity, namely, an acute inflammatory response and a repair process Different noxious stimuli evoke a similar picture, which is apparently due to a constant pathological response of the arterial media Consequently, it cannot always be concluded that the experimental lesions are caused by mechanisms similar to those of their clinical counterparts.

RESULTS OF EXPERIMENTAL ATHEROSCLEROSIS

Degenerative changes, mainly limited to the intima, are characteristic of atherosclerosis, extension of the changes into the media, however, are so common that many authors suggest that atherosclerosis may really start in the latter. Furthermore, although the process may seem to be primarily of a degenerative nature, the role of inflammation has not been completely ruled out in some instances (Saphir and Gore). For brevity's sake, it will be assumed that (1) the arterial changes of atherosclerosis develop primarily *in the intima*, and (2) inflammation is *not* a primary phenomenon in the majority of the atherosclerotic lesions.

It will be useful to review the various methods of production of atherosclerosis in different species

Rabbit. The rabbit is the first animal in which atherosclerotic lesions have been consistently produced, the fact that the lesions were first obtained by feeding cholesterol has greatly influenced later research. Cholesterol is a foreign substance to herbivora which, after weaning, do not normally ingest this solid alcohol. When cholesterol is given in amounts varying from 250 to 1,000 mg per day for 2 or 3 months, a marked hyperlipemia and hypercholesterolemia is produced, and gross atherosclerotic lesions appear in 70 to 80 per cent of the animals, at the same time, xanthomatous deposits in the pulmonary circulation, cartilages, cornea, and liver, as well as amyloidosis of the skin, ectopic blood formation, and other signs of damage can also be found. The fact that 20 to 30 per cent of the cholesterol-fed rabbits are naturally resistant to this form of atherosclerosis must be remembered when experiments consisting of a few animals are statistically analyzed. The way in which cholesterol is given does not influence the severity of the lesions although the iodide number of the accompanying oil does influence the amount of the change. The early lesions induced by this method consist of sudanophilic droplets located in the subendothelial ground substance of the intima and may appear even before the occurrence of pronounced changes in the plasma level of lipids, alternative explanations suggest that cholesterol is first phagocyted by the endothelial lining cells and then released into the ground substance. However, the subsequent gross hypercholesterolemia undoubtedly influences the deposition of cholesterol in the intima and the subsequent arterial reactions. As a whole, it seems well established that feeding cholesterol to rabbits induces local changes in the intima and in the media (increased endothelial permeability, increased subintimal mucopolysaccharides, appearance of a phagocyting capacity of the endothelial cells) and that subsequently the cholesterol-loaded plasma, by a process of ultrafiltration, is able to cause local deposits, proliferation of foam cells, fibroblasts, and other damage. Older theories trac-

Experimental arteriosclerosis and atherosclerosis

M. MALINOW

Degenerative changes of the arterial walls have been produced by different methods and in many species. Thus, several questions arise in connection with the significance of these findings:

1. Are the degenerative lesions of different species of animals equivalent?
2. What mechanisms are involved in producing these lesions?
3. Is it possible to influence, therapeutically or otherwise, the induced lesions?
4. Can the results of animal experiments be applied to man?

For the last one-half century, myriads of experiments have been performed in trying to answer these questions and, although some points have been clarified, others still need further research

All arterial degenerative changes can be grouped under the name of *arteriosclerosis*, while the term *atherosclerosis* refers only to lipid infiltration and cellular proliferation, mainly centered in the intima. The pathological changes are probably equivalent in different species of animals when the histological picture is similar, this also applies to man Naturally, there are reservations in regard to the extension to human beings of experimental results obtained in animals Furthermore, it is recognized that, although lesions may be morphologically identical, the mechanisms involved in their production may not be identical in different species.

The "degenerative" lesions are not sharply delimited, but it is customary to separate from them certain pathological processes, such as acute necrotizing arteritis, the fibrinoid changes seen in the "collagen diseases," and others. Consequently, these arterial lesions will not be considered. Although the pathological picture (and the pathogenic mechanisms?) of the degenerative lesions in the systemic and in the pulmonary circulations may be similar, this discussion shall be limited to the systemic circulation Many of the conclusions that will be reached for the systemic arteries can possibly be extended to the lesser circulation.

METHODS USED FOR CAUSING EXPERIMENTAL ARTERIOSCLEROSIS

Different methods can be used to cause an injury to the arterial media, a subsequent acute inflammatory response, and an associated process of repair similar to those of human arteriosclerosis.

Direct Trauma. Vascular scars have been produced in rabbits and dogs by freezing the abdominal aorta, cauterization of the vasa vasorum (Schlichter et al., 1949), injection of irritating substances into the arterial wall, and by various tearing or cutting maneuvers. When local trauma was combined with a systemic factor, such as a high-cholesterol diet, the injection of egg yolk or of a cholesterol suspension, something similar to the atherosclerotic process may result, supporting the concept that human atherosclerosis may result from changes initiated in the media.

Kidney Trauma. Nephrectomized dogs maintained for prolonged periods either by peritoneal dialysis or an artificial kidney (especially if previously fed on a high-fat diet) show degeneration

of the smooth fibers of the media and hyalinization and proliferation of the subintima; these

gery, a peculiar type of medial calcification follows, this has been attributed to the development of hyperparathyroidism secondary to the kidney insufficiency. All these experiments point to the fact that a normally functioning kidney is necessary for the maintenance of the integrity of the medial layer of the arteries.

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ENDOCRINE GLANDS. Rats with diabetes caused either by alloxan administration or by subtotal pancreatectomy show arteriolar hyalinization, it is possible that these changes are dependent not on the pancreas but on a secondary kidney damage.

OTHER FACTORS. The intravenous injection of allylamine into dogs induces fibrinoid necrosis of the coronary arteries as well as slight changes in the aortic intima. when egg yolk is also injected, fatty infiltration is observed and a lesion similar to human atherosclerosis may result.

From the above results it appears that, although an injury to the arterial media can be produced in many ways, the histological picture may show a great uniformity, namely, an acute inflammatory response and a repair process. Different noxious stimuli evoke a similar picture, which is apparently due to a constant pathological response of the arterial media. Consequently, it cannot always be concluded that the experimental lesions are caused by mechanisms similar to those of their clinical counterparts.

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ing the foam cells to detached Kupffer cells have been discarded.

Contrary to the above-mentioned findings, marked hyperlipemia without hypercholesterolemia does not produce atherosclerosis in rabbits, thus pointing to the pathogenic role of cholesterol in this connection. Other foreign sterols, such as dihydrocholesterol, when given in sufficiently high doses, can also produce atheromatous lesions, the precipitation of foreign sterols in the arteries of rabbits, then, is apparently a nonspecific phenomenon probably related to solubility factors and other conditions.

Chicken. Chickens develop spontaneous atherosclerosis and these lesions have also been experimentally induced through cholesterol feeding, stilbestrol implantation, or dihydrocholesterol feeding. Thorough studies have been made, especially on the first of these methods. They were able to show that cholesterol-fed birds are resistant during the very early period of life, while the lesions are easily produced after the eighth week and regress spontaneously after the twentieth. This points to the importance of endogenous factors on the metabolism of exogenous cholesterol and on the subsequent arterial lesions. The same method has been used to demonstrate complex endocrinous relationships between the development of arterial lesions and the function of the adrenals, pancreas, thyroid, and gonads. An important fact that has emerged from these studies is that estrogenic substances may prevent and cause regression of coronary atherosclerosis (Katz and Stamler, 1953).

Dog. Lesions resembling atherosclerotic plaques have been produced in dogs by the intravenous injection of huge amounts of macromolecular substances (gum acacia, polyvinyl alcohol, etc.), which apparently are phagocytized by the endothelial cells True atherosclerotic lesions were produced later in cholesterol-fed, hypothyroid dogs (Steiner and Kendall) The early lesions consisted of lipid deposits in the media, between and within the cells, followed by a secondary intimal proliferation. In contrast with this, spontaneous lesions arise as early degeneration of the internal elastic membrane with a secondary proliferation of intimal connective tissue, while lipid deposits are apparently a secondary phenomenon, hypertension increases the severity of atherosclerosis in dogs.

Rat. Until recently rats have been considered to be resistant to the development of atherosclerosis. It was demonstrated that this "resistance" was not a property of the arteries themselves, since aqueous buffered suspensions of cholesterol, when injected into doubly ligated femoral arteries, produced atherosclerotic-like lesions in rats Shortly afterwards, experimentally induced generalized atherosclerosis was reported by three independent groups; later on, spontaneous atherosclerosis was described. The rat, being an omnivorous mammal with a diet similar to that of man, could be considered suitable for studies of a chronic disease Its short life span would make it quite desirable, but the minuteness of the lesions forces the researcher to rely exclusively on microscopic studies, except when synthetic diets, with a high content of cholesterol and cholate, are given to hypothyroid rats. In this case, gross aortic lesions are consistently produced. Along these lines, it has been shown that hypertension has no aggravating effect on the development of atherosclerosis and that estrogens can prevent spontaneous and experimentally induced atherosclerosis.

Cat. Spontaneous atherosclerosis in the aorta and the coronary arteries of cats has been described. The lesions apparently start as medial elastic fragmentation, lipids playing no part in the early process.

Monkey. Atherosclerosis has been produced in two types of monkeys: (1) the *rhesus*, through pyridoxine deficiency or prolonged high-fat, high-cholesterol diet, and (2) the *Cebus*, through mild deficiency of organic sulfur compounds plus a large cholesterol intake. In pyridoxine deficiency, there is an accumulation in the intima (and sometimes the media) of the abdominal aorta and the iliac arteries of a mucoid intercellular substance showing the metachromatic staining of mucopolysaccharides, there also is a proliferation of endothelial cells and elastic fibers while, in older lesions, lipoid deposits appear. When other dietary methods are used, excess lipids are deposited in the arteries, and endothelial plaques are plentiful.

Other Animals. Atherosclerosis has also been described in several other animals including the golden hamster, guinea pig, elephant, goose, mouse, thus showing that atherosclerotic lesions are not the exclusive property of any species

PATHOGENETIC MECHANISMS OF EXPERIMENTAL ATHEROSCLEROSIS; POSSIBLE CONNECTION WITH HUMAN ATHEROSCLEROSIS

The fact that atherosclerosis can be produced in many species through different methods clearly shows that these lesions can be considered to represent nonspecific end results following arterial injuries, although it must be granted that not every type of injury leads to the development of atherosclerosis Some of the initiating factors, such as pyridoxine and deficiency, stilbestrol implantation, are clearly

not connected with human atherosclerosis; others, such as high-fat diet, high-cholesterol diet, or a combination of both, have not been conclusively shown to be concerned with the initiation of lesions, while still other factors (e.g., genetic, constitutional), although probably important, are still undetermined. Nevertheless, and in spite of the lack of knowledge of the mechanisms involved in the factors responsible for the *initiation* of the atherosclerotic process, it is apparent that the *progression* of the lesions is somewhat connected with a disturbance in the metabolism of lipids, even though other factors may be involved. The factors related to the progression (and to the initiation?) of the degenerative changes can be classified as follows.

Local Factors. Arteries must not be regarded as simple tubes only able to distribute blood, but as complex organs within which complicated enzymatic reactions do take place. Furthermore, materials enter and leave the arterial walls. They are carried by fluids which follow hemodynamic laws similar to those operating in the rest of the organism: fluids ultrafilter toward the arterial wall from the intima and from the arterial side of the vasa vasorum and are subsequently reabsorbed from the artery through the venous side of the vasa vasorum, as well as from the lymphatics. This ultrafiltration must also depend on the permeability of the endothelia, the filtration pressure (arterial and capillary), the osmotic pressure, and the tissue pressure (Part 2, Chap. 18). Moreover, if lipids are transported within the arteries as they are in the intestines, the lymphatics may play an important role in the pathogenesis of atherosclerosis, a point seldom raised in this connection. It is clear that the accumulation of any substance within the arterial wall must necessarily be secondary to a disturbance of the intramural circulation, of the local metabolism of the substances normally carried to the artery, or both. As a consequence, atherosclerotic plaques, which represent the accumulation of different lipids within the arterial walls (cholesterol, phospholipids, and neutral fats) could be the result of the following factors: (1) an increased input load, due to higher plasma levels or greater velocity of filtration, caused by either higher pressure or increased permeability of the endothelia, (2) an increased local synthesis, (3) a decreased local utilization; (4) a decreased removal due to local precipitation through physical instability or disturbance in the reabsorbing system; or (5) a variable combination of these processes.

Increased plasma-cholesterol level is only one of the many factors which lead to accumulation of this material within the arterial walls. This explains the many examples of atherosclerosis in spite of a normal cholesterolemia. Furthermore, it must be remembered that most of the clinical importance of atherosclerosis is related to the obstruction of the blood flow effected by this process. The formation of intimal plaques is only one of the mechanisms which may ultimately lead to the "atheromatous obstruction" of an artery. Consideration must also be given in this connection to local thrombus formation, intramural hemorrhage, and vascular muscular contraction.

General Factors. General factors, such as hypercholesterolemia, hypertension, diabetes, and sex, which are related to the progression (and the *initiation?*) of atherosclerosis, must *necessarily influence* the plaques through a modification of the local factors already mentioned.

DISTURBED LIPID METABOLISM. High blood lipid levels, indicative of a disturbed general lipid metabolism, are connected with an *acceleration* of atherosclerosis, although not all lipids share similar actions. An elevated blood-cholesterol level is necessary for the development or the acceleration of atherosclerosis in some animals (rabbits, dogs, chickens, monkeys) but not in others (rats). In rabbits, elevated levels are apparently secondary to a failure of the hepatic Kupffer cells to dispose of the absorbed intestinal cholesterol and to transfer it to the liver cells. In man, the cholesterol synthesized from the acetyl coenzyme A formed during metabolism is probably more important than exogenous cholesterol. Furthermore, synthesis in the arteries may also contribute to the local accumulation of the atheromatous plaques. Induced high blood levels of *neutral fats*, even when accompanied by a moderate increase in cholesterol level, are not connected with an accelerated atherogenesis; this suggests that cholesterol is solubilized in the neutral fat. Heparin, which clears postprandial lipemic blood and activates a lipolytic enzymatic system in the plasma, has been re-

ported to decrease cholesterol-induced atherosclerosis in rabbits. High *phospholipid* levels apparently are able to protect animals from the development of atherosclerosis, and this is also explained as due to a solubilizing effect. Furthermore, attention has been drawn, not only to the absolute levels attained by individual lipids in the blood, but also to their physicochemical distribution. Lipids are not soluble in plasma and are transported as complex combinations with the plasma proteins. It has been postulated that not all these lipoproteins share the same "atherogenic" action, this being maximal for the S_f 12 to 400 lipoproteins[1] (Gofman, 1950) This concept has been questioned in individual cases and it has been suggested that more useful information can be gathered from the level of blood cholesterol. As already pointed out, hypercholesterolemia is just *one* factor which may lead to increased cholesterol deposition within the arterial walls.

HYPERTENSION. The clinical observation that hypertension accelerates atherogenesis has been confirmed in several kinds of animals (rabbits, dogs, and chickens). In rats, however, hypertension does not seem to influence atherosclerosis.

SEX. The gonadal hormones are able to influence experimental atherosclerosis, but the results are not the same in different animals. Most studies have been conducted with female hormones, following the studies of Pick Diethylstilbestrol increases aortic atherosclerosis while estradiol benzoate prevents or causes regression of coronary atherosclerosis in cholesterol-fed chickens. A somewhat similar situation exists in rats, where estradiol benzoate cannot prevent coronary atherosclerosis in nephritic rats on high-fat diets, but prevents the development of spontaneous atherosclerosis in other parts of the vascular system In rabbits, both estrogens and testosterone can prevent atherogenesis in the female, but not in the male. In man, estrogenic substances decrease coronary atherosclerosis

PARTS OF THE ARTERIAL SYSTEM. Besides the stated difference between systemic and pulmonary circulation, experimental atherogenesis does not proceed in a parallel way in all parts of the systemic circulation. For instance, estrogens increase atherosclerosis *in the aorta* while decreasing the lesions *in the coronary system* of cholesterol-fed chickens. The same estrogenic substances can prevent atherogenesis under certain circumstances in the aortic collateral arteries but not in the coronary arteries of perinephritic rats. These experiments again point to the importance of local factors and class differences in the genesis of arterial lesions.

In summary then, the pathogenesis of the arterial intimal lesions is not known. From the fact that they can be produced by different methods, they can be considered as representing nonspecific end results caused by several noxious stimuli, the reaction of the arterial wall being regulated by the interplay of local and general factors One of the many possible noxious stimuli acting in this connection is an abnormal metabolism of the lipids, chiefly cholesterol. This leads to increased deposition of cholesterol in the arterial walls and eventually causes a localized tissue reaction, *the atheromatous plaque.*

THERAPY OF EXPERIMENTAL ATHEROSCLEROSIS

An important fact which has emerged from research is that atherosclerotic lesions can be prevented or may regress under favorable circumstances Of course, experimental results obtained in one species and by the use of a particular method cannot always be applied to another species in which atherogenesis may follow a totally different method

In interpreting results of "curative" drugs in connection with atherosclerosis, other points must be taken into consideration. For instance, when cholesterol is given, it must be determined if it is actually ingested when given in combination with another drug which may be offensive to the animal or interfere with its eating (unpalatable) or sleeping habits. Another complicating factor is the total quantity of calories ingested, since undernutrition may increase or decrease atherogenesis in different species of animals.

Iodides and Thyroid Hormones. Desiccated thyroid gland decreases atherogenesis in chickens while iodine, which had been reported as protecting rabbits against cholesterol-induced atherogenesis, has been demonstrated to be without effect.

[1] S_f is the symbol for *Svedberg unit of flotation*

Lipotropic Agents. Lipotropic agents have consistently failed to alter experimental and spontaneous atherogenesis in rabbits and chickens

Heparin. Heparin, which is able to activate a lipolytic system in the blood, has been tested in the treatment of experimental atherosclerosis The results are somewhat conflicting since it has been reported that heparin does not prevent atherogenesis in the rabbit or in the chicken, although it seems that, under certain conditions, it can prevent it in other cholesterol-fed animals.

Estrogens. Estrogens have successfully prevented coronary atherosclerosis in cholesterol-fed chickens, and these results have been confirmed in rats, in which they are also effective in other parts of the arterial tree. In female, but not in male cholesterol-fed rabbits, estrogens or testosterone can prevent aortic atherogenesis The mechanisms involved are not clear in this species since some authors believe that the preventive action is mediated through the ovaries, while others state that castrated female rabbits show less atherosclerosis than nonoperated controls

Other Factors. Attempts to prevent absorption of intestinal cholesterol have been reported successful in decreasing atherogenesis in cholesterol-fed rabbits and chickens. A cholesterol-free brain fraction, which apparently is able to promote the conversion of the absorbable cholesterol into nonabsorbable coprosterol, decreases atherosclerosis in chickens. *Sitosterol*, which apparently competes with intestinal cholesterol for enzymatic esterification and subsequent reabsorption, seems to prevent atherogenesis in cholesterol-fed rabbits and chickens Finally, *dihydrocholesterol* (an alcohol greatly resembling cholesterol) can prevent the intestinal absorption of cholesterol and the subsequent atherosclerosis in cholesterol-fed rabbits and chickens, even though prolonged administration of this sterol induces atherosclerosis in the latter.

Other substances have been reported to have various results in the treatment of cholesterol-induced atherosclerosis, such as gallogen, elastase, ferric chloride, and adenyl monophosphate Some of these have already been discarded, others must be further evaluated Nevertheless, since practically all are tested against cholesterol-induced atherosclerosis, a similarity of the mechanisms of experimental and human atherosclerosis should be demonstrated before they can be applied to man.

4

Biochemistry of arteriosclerosis

JOHN W. GOFMAN

A subject such as the biochemistry of arteriosclerosis can be approached in two different ways. The first is the encyclopedic approach of listing the contributions to biochemical morphology of the arteriosclerotic lesion. This provides a recapitulation of important contributions of investigators, past and present, throughout the world, but has no real value to the practicing physician. The second is to seek out those features of the biochemistry of arteriosclerosis which lend themselves to the formulation of a reasonable "model" of the development of arteriosclerosis that may be meaningful in clinical medicine.

Perhaps in a set of volumes such as these it is necessary to review what is meant by a "model." By this is *not* meant a final, completed concept of a thoroughly understood phenomenon, but rather what appears to be a reasonable construct of the biochemical features of the disease, integrated into a formulation that allows clinicians and researchers alike to go forward with further studies and evaluations. A "model" is set up as a target for criticism, for tests of consistency with reality (as revealed by observational medicine), and for modification. Such a "model" is not created out of sheer speculation, but with some imagination utilized to weave together a body of solidly established biochemical and clinical *facts* concerning the disease under study, here arteriosclerosis. This weaving is necessarily imperfect for, if *every* facet of *every* part of the problem were completely understood, no weaving would be necessary; one could instead be completely encyclopedic. Thus, it is the hope of the author that the following biochemical "model" of arteriosclerosis will serve as a target for the critical analysts of the problem, who will be able to detect where the weaving together of certain observational *facts* has been imperfect and where a reweaving can serve to improve the model, so that it can better serve our ultimate goal—an understanding of the evolution of arteriosclerosis which can aid medicine in its prevention or minimization.

THE LESION

Two subjects are of real consequence in a discussion of the arteriosclerotic lesion: (1) its structural features of importance; (2) its focal character.

The chemical, histochemical, histological, and gross anatomic features of arteriosclerosis have been intimately described (Chaps. 1, 2, 3). That lipid alterations, mucopolysaccharide alterations, fibrosis, elastic-tissue changes, thrombosis, hemorrhage, and calcification are all important structural elements is not to be questioned, they represent observational facts. How these structural features mesh together is today a matter of speculation and a challenge for further work. However, these structural elements of the arteriosclerotic lesion do mesh together and, whatever the primary or initiating cause of the lesion, it is clear that the clinical consequences of arteriosclerosis are felt when one or more of these structural elements has led to an appreciable *degree of narrowing* of the arterial lumen, be it in the coronary, the cerebral, or the peripheral arterial tree. The nomenclature of Goldblatt, i.e., *simple intimal arteriosclerosis,* encompasses those lesions in important areas of the arterial tree which are productive of luminal encroachment and have ultimate clinical consequences, and avoids the fruitless arguments (fruitless at this time) as to which structural elements

are primary or of more importance than others The lesion of interest is that which leads to clinical consequences and, hence, the final concept of primacy or importance of structural features must meet the test of consistency with clinical, observational reality. Luminal narrowing, acute or chronic, appears to meet such a test at present Most other features have hardly even been considered.

The *focal* character of arteriosclerosis is clearly a reality to any observer. No one can doubt the truth of the statement that one region of a particular arterial bed may be more extensively diseased than the region a centimeter farther along the same artery, or can doubt that, at times, one arterial bed itself, e g., the coronary bed, can be extensively diseased while another will be but little involved. Unfortunately these facts have been widely misused to confuse the physician about two critical features of the development of arteriosclerosis First, while intimal arteriosclerosis is characterized by an ability to manifest major *focal* features, there does exist a tendency for the degrees of involvement of various parts of a single arterial bed, as well as for the degrees of involvement of widely separated arterial beds, *to rise and fall together* Second (and in part a corollary to the first point), the focal character of the arteriosclerotic lesion *in no way* militates against the evidence, now difficult to assail, that general metabolic features operate to determine the degree of arteriosclerotic involvement of muscular and large arteries in arterial beds throughout the body.

Every effort must be encouraged to delineate the important features which are determinative of the focalization of the lesion Proposals that mechanical or anatomic factors (such as kinking, local wall defects, or elastic tissue degeneration) or toxic factors (such as the action of catechol amines) are major elements in human intimal arteriosclerosis are dubious ones that need to be decided in the early future. Further work will undoubtedly help in this area, for no definitive case has yet been made out for any of them

Whatever the ultimate solution of the problem of focalization, there is no conflict of this aspect of the problem with that of the general metabolic features of the development of this disease There seems to be little reason to doubt that focal factors would be of minor moment in the production of arteriosclerosis if the intensity of the general metabolic predisposing influences could be brought under control. This is hardly equivalent to the statement that arteriosclerosis would be completely prevented if the general metabolic influences were controlled. *Rather, such an event would grossly reduce the incidence of development of lesions of sufficient consequence to produce widespread clinical manifestations.*

GENERAL FACTORS INVOLVED IN PRODUCTION OF THE LESION

It is in the area of general factors involved in the production of the arteriosclerotic lesion that methods have been developed over the years that allow for approaches to the clinical consequences of the lesion These consequences have been elucidated in three major ways over the years:

1. By experimental induction of lesions in animals that simulate closely many features of the human lesion

2 By direct study in human beings of clinical entities that are consequences of arteriosclerosis, especially coronary heart disease, arteriosclerosis obliterans, and cerebrovascular disease

3. By pathological studies of the human arteriosclerotic lesion in various vascular beds.

Out of such studies certain conclusions can be drawn; these appear safely established and are unlikely to change in the course of further integration of existing knowledge with new observational material Arteriosclerosis in the human being is a *progressive, cumulative disease*, that is extremely widespread in populations throughout the world, with great variability in the extent of its development characterizing certain population subgroups, e g., males of a particular age in a single geographic locale. The pathological character of the lesion at any moment is the sum of the fresh increments to the lesion plus older increments that have undergone certain changes during the course of their existence within the arterial wall The net effect of all such increments, new and old, is production of an encroachment upon the arterial lumen. No reason exists to differentiate intimal arteriosclerosis in young individuals from intimal arteriosclerosis in old individuals. Any existing difference resides primarily in the altered proportions of relatively

fresh increments in comparison with older ones. Reversibility of the arteriosclerotic lesion is clearly established in experimental animals and, by indirect evidence, appears to be a highly probable occurrence in human beings as well. So-called *episodic* development of human arteriosclerosis seems to be the result of periodic accelerations in the rate of development of the lesions, over and above a steady cumulative process.

Inasmuch as arteriosclerosis is *a cumulative process over time*, there must exist at least one *rate factor* which is important. It can be anticipated that a high *rate* of cumulation will result in extensive disease development in relatively few years, a low rate of cumulation would mean that many more years would be required to produce the same development of lesions A most profitable approach to the biochemistry of arteriosclerosis is to seek out factors that may determine, in part or in whole, *the rate of development of the lesion* A host of factors has been considered, suspected, and speculated upon, but only two have remained which are definitively implicated as rate factors in the development of arteriosclerosis: (1) the level of certain blood lipids; and (2) the level of the blood pressure These are *independent* rate factors in the development of arteriosclerosis. By this is meant that each provides information concerning the rate of lesion development over and above information provided by the other. Thus, if two persons were identical with respect to the crucial blood lipids, but one showed a higher diastolic blood pressure than the other, the rate of arteriosclerosis development would be higher in the former in proportion to the elevation in blood pressure. Conversely, if two persons were identical with respect to habitual blood pressure, but one showed a higher level of the crucial blood lipids than the other, the rate of development of arteriosclerosis would be higher in the former person in proportion to the degree of elevation in the level of the blood lipids It is of interest to note that the concept of arteriosclerosis presented here is essentially that proposed by Virchow many years ago, namely that filtration of blood lipids probably initiates the arteriosclerotic lesion, abetted by the pressure of the blood in the vascular lumen. Virchow's astute suggestion was made in the absence of a great deal of substantiating data, clinical or experimental, simply because it appeared reasonable to him After many decades of relatively barren wandering in this medical area, investigators admit that multiple evidence provides a firm support for Virchow's original concept.

THE BLOOD LIPID FACTOR

It was stated above that only certain blood lipids are of crucial importance in determining the rate of development of arteriosclerosis. This is verified by direct observation that indeed certain other blood lipids are either (1) *uninvolved* in the development of arteriosclerosis or (2) possibly *inversely related* to the development of arteriosclerosis. Essentially, all the lipids in the blood exist in the form of macromolecular complexes either with polypeptides or proteins, and are therefore designated as *lipoproteins*. These lipoproteins may be detected and quantitated by a variety of methods, ranging from the original chemical precipitation techniques of Macheboeuf to the precise methods of *ultracentrifugation*. Between these extremes there is a variety of methods for identifying and quantitating the lipoproteins of blood. All are of value, but some are more crude with respect to information than others.

The cardinal fact is that certain liproproteins *exist* in blood. If these lipoproteins are assayed by a particular method, no amount of chemical, physical, or statistical maneuvering will extract additional information from that analysis of the blood lipid content. The real difference between the various methods lies in the differing extent to which they assess the blood content of the particular lipoproteins of interest in arteriosclerosis. This point deserves illustration, for few issues have more thoroughly beclouded the status of our knowledge of the relationship of blood lipids to the development of human arteriosclerosis.

Cholesterol and the *phospholipids* are two of the kinds of substances which exist in the blood wholly in the form of lipoproteins Every lipoprotein class isolated from human blood contains some cholesterol and some phospholipid The percentages of cholesterol and phospholipid differ from one lipoprotein class to another Many investigators have come to the conclusion that *high cholesterol/phospholipid ratios* are in some way associated with a high rate of development of human arterio-

sclerosis. But they have drawn the incorrect conclusion that there is something intrinsically important about the ratio of these two substances in the blood. The reason why the cholesterol/phospholipid ratio is of importance at all in arteriosclerosis (or some of its clinical sequelae) is that *there is an appreciable correlation between the cholesterol/phospholipid ratio and the levels of those low-density lipoproteins* which are intimately related to the rate of development of arteriosclerosis. However this correlation is highly imperfect. Numerous situations exist where the cholesterol/phospholipid ratio is favorable while the low-density lipoprotein pattern is highly unfavorable. In such cases, the ratio of cholesterol to phospholipid *erroneously* predicts a low rate of development of arteriosclerosis. Other situations exist where the cholesterol/...

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... cholesterol content, and the turbidity of serum. All of them are secondary methods that approximate a measure of those lipoproteins in blood that are of demonstrable importance in arteriosclerosis. If this is realized, there is no objection to the employment of any of these lipid assays in the evaluation of arteriosclerosis. Concrete evidence has been brought forth of an association between the rate of development of arteriosclerosis and the group of lipoproteins characterized ultracentrifugally as *the S_f 0 to 400 lipoproteins*, these are part of the over-all group of substances in the blood known as *low-density lipoproteins*.

Unfortunately, when electrophoretic techniques are used, these lipoproteins are labeled as beta lipoproteins under certain analytical conditions and as alpha lipoproteins under other conditions. Under still other conditions, electrophoretic analysis completely misses some of the S_f 0 to 400 lipoproteins, either as beta or alpha lipoproteins. Hence, if electrophoretic classification is to be used at all, it is imperative that the conditions be precisely defined, if two investigators are desirous of comparing the results of their respective investigations of arteriosclerosis.

Ultracentrifuge methods, under standard conditions, are free of the various difficulties inherent in the more crude methods described above. A *direct* assay of the lipoproteins *in the S_f 0 to 400* band is readily available through ultracentrifuga-

cation will become available through some other technique in the future, possibly even the early future. However at present, no method provides the requisite information as directly as do the methods involving the ultracentrifuge.

Utilizing coronary heart disease and arteriosclerosis obliterans as criteria for arteriosclerosis of their respective arterial beds, it has been shown that the levels of the S_f 0 to 400 lipoproteins are directly related to the *rate* of development of arteriosclerosis. The relative importance of various subclasses of lipoproteins within the S_f 0 to 400 band is still subject to revision as additional evidence becomes available. For *coronary arteriosclerosis, the best estimate indicates that the S_f 12 to 400 segment is approximately one and one-half to two times as important, milligram for milligram, as the S_f 0 to 12 lipoprotein segment.* This has led to the formulation of a combined value which allows for this weighted importance of the two subclasses, *the atherogenic index*. *Atherogenic index is* defined as equal to

$$\frac{L_1 \text{ (in mg/100 ml)} + 1.75\ L_2 \text{ (in mg/100 ml)}}{10}$$

where L_1 = lipoproteins of S_f 0 to 12

L_2 = lipoproteins of S_f 12 to 400

That both lipoprotein classes (S_f 0 to 12 and S_f 12 to 400) are of independent importance as determinants of the rate of development of human arteriosclerosis is quite clear. That the 1.75 factor for weighting the S_f 12 to 400 lipoproteins is subject to revision is also quite clear. Furthermore, it is possible that the relative weighting factor may be different for arteriosclerosis in *one* arterial bed as com-

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or wholly explainable by the proved observations that, on the average, *women present lower lipoprotein and blood pressure levels early in adult life than do men, equal levels somewhat later in life, and higher levels than men in the late decades of life.*

Age. The extent of arteriosclerosis and the incidence of coronary heart disease rise progressively with increasing age, in both the men and women. This is almost wholly or wholly explained by the *cumulative* operation of both the blood lipoprotein and blood pressure factors over a period of years

Family History. That certain families are characterized by excessive rates of development of arteriosclerosis and a high incidence rate of coronary heart disease can readily be documented It has been shown in studies of a cross section of the population that a history of premature heart disease in the father is associated with an elevation in atherogenic index and, to a much lesser extent, with an elevation in the average diastolic blood pressure of the offspring These effects operate, not only in families with extreme blood lipid disorders, but also in those with more moderate ranges of blood lipoprotein levels

Overweight. The studies of Dublin and of Dauber show a higher incidence rate of coronary heart disease in overweight persons than in those of ideal, or less than ideal, weight Furthermore, pathological studies show a higher quantitative degree of coronary arteriosclerosis in overweight persons than in nonoverweight persons All these findings are quantitatively explainable by the combination of the effect of overweight in raising both the average value of the atherogenic index and the average blood pressure level. No evidence has been brought forward to implicate the overweight per se as a mechanical-load factor in the explanation of these phenomena.

Diet. Dietary factors have been implicated, from a variety of sources of evidence, in the development of arteriosclerosis and clinical coronary heart disease Essentially all investigators in this area are convinced that dietary effects are primarily mediated by the effects of certain dietary constituents upon the levels of several lipoprotein classes Some suspicion exists that perhaps diet may also operate partly by an effect upon blood coagulability. Diet can influence blood pressure levels as well

Two major classes of foodstuffs have been indicted for their effect upon blood lipid levels: (1) the *saturated animal and vegetable fats,* both of which can increase the S_f 0 to 12 and S_f 12 to 20 lipoprotein levels (and thereby the blood cholesterol level); and (2) *the carbohydrates,* which can increase the S_f 20 to 100 and S_f 100 to 400 lipoprotein levels (and thereby the total blood lipid level). It has been proved conclusively that these two dietary elements are the responsible agents, not the caloric intake they represent.

Cigarette Smoking. Hammond and Horn have conclusively shown that the incidence of clinical coronary heart disease is appreciably higher in regular *cigarette smokers* than in nonsmokers. This effect is almost wholly or wholly explained by (1) an association of *elevation of the atherogenic index* with regular cigarette smoking; and (2) by the acute effect (during smoking) of cigarettes upon blood pressure levels. There is no chronic, sustained effect of cigarette smoking on average blood pressure levels. The effect of cigarette smoking upon the serum lipoprotein level and atherogenic index appears reversible, since those who have spontaneously ceased smoking cigarettes show blood lipid levels indistinguishable from those of persons who have never smoked. It is of interest that the studies of Hammond and Horn show that cigarette smokers who have ceased smoking regain part of the protection against coronary heart disease which characterizes nonsmokers. Since some of the accumulated coronary arteriosclerosis is most likely irreversible, it is readily understood why former smokers do not regain *all* the protection possessed by nonsmokers, even though their lipoprotein levels revert to those of the latter

Diabetes Mellitus. The quantitative increase in the incidence of coronary heart disease in diabetics as compared to the population at large and the relatively greater magnitude of this increase in the diabetic woman compared [illegible]

[illegible] lipoprotein–atherogenic index elevation and blood pressure elevation in diabetics, contrasted with the population at large. In severe decontrol with acidosis, diabetic patients in general show *massive* elevations in the blood content of several lipoprotein classes

pared with another, e.g , coronary versus peripheral.

THE BLOOD PRESSURE FACTOR

Virchow long ago had theorized that, the higher the blood pressure, the higher would be the rate of filtration of lipids from the blood into the arterial wall, and hence the greater the rate of development of arteriosclerosis. Whether or not his surmise concerning filtration was correct, clear-cut evidence now supports his concept that the higher the blood pressure, the greater is the rate of development of arteriosclerosis. This evidence has been gathered in three areas of research:

1 Experimental animal research, both in the dog and the rabbit, has demonstrated that, all other factors being equal, the rate of development of arteriosclerotic lesions varies directly with the arterial blood pressure level.

2 The careful study of a major clinical consequence of coronary arteriosclerosis, namely coronary heart disease, has led to the same conclusion by several investigators; i.e , the higher the blood pressure, the greater the risk of future clinical coronary heart disease. Taken together with the other pertinent evidence, the most reasonable basis for these observations is that elevation of blood pressure accelerates the rate of development of coronary arteriosclerosis.

3. It has been demonstrated most directly in the human being by Young et al. that, the higher the blood pressure is during life, the greater will be the extent of arteriosclerosis found postmortem in both the coronary and the cerebral arteries. Indeed, considering the *variability* of blood pressure measurements, the extent of quantitative relationship between degree of arteriosclerosis and blood pressure level is great

COMBINATION OF THE BLOOD LIPID FACTOR AND THE BLOOD PRESSURE FACTOR

In the foregoing discussion it was pointed out that (1) developing arteriosclerosis progresses, on the average, at a rate proportional *to the blood concentration* of certain lipoproteins (those within the S_f 0 to 400 class), and (2) this progression continues, on the average, at a rate proportional to the level of the diastolic blood pressure. However, on other grounds, it is known that the diastolic blood pressure is only very slightly correlated with the blood lipoprotein level. That is, a person with a high blood pressure can have low, moderate, or high lipoprotein levels, and conversely a person with a high lipoprotein level can have a low, moderate, or high blood pressure. Quantitative analysis of this problem has shown clearly that the blood pressure provides information concerning arteriosclerosis development *independent* of that provided by the lipoprotein level. The best estimate of the combined effect of both variables resides in the statement that arteriosclerosis development proceeds at a rate proportional to the *product* of the diastolic blood pressure and the lipoprotein level. It is clear, therefore, that an individual low in both multiplicative factors will show the lowest rate of development of arteriosclerosis; a person high in one factor and low in the other will show an intermediate rate; and a person high in both factors will show the highest rate of development of arteriosclerosis. Further, the advantage conferred by a low blood lipoprotein level can be quantitatively offset by a high blood pressure level, and vice versa.

OTHER FACTORS INVOLVED IN THE DEVELOPMENT OF ARTERIOSCLEROSIS

Over the years, a variety of other factors have been suspected or proved to be associated with the rate of development of human arteriosclerosis. Careful analysis of all these factors indicates that none of them can yet be shown to possess the independent status of the blood lipoprotein and the blood pressure factors The relationship of each of them to the development of arteriosclerosis has been tested with reference to the main clinical sequela of human arteriosclerosis, namely, coronary heart disease. In every case, the major share or all of the quantitative relationship of the "other factor" to coronary heart disease is explainable by its effect upon the blood lipoprotein level (as expressed in the atherogenic index formulation), the blood pressure level, or both

Sex. In early and middle adult life women show a lower degree of coronary arteriosclerosis as well as a lower incidence rate of coronary heart disease than do men. Later in life the sexes approach equality with respect to both phenomena. These facts are almost wholly

or wholly explainable by the proved observations that, on the average, *women present lower lipoprotein and blood pressure levels early in adult life than do men, equal levels somewhat later in life, and higher levels than men in the late decades of life.*

Age. The extent of arteriosclerosis and the incidence of coronary heart disease rise progressively with increasing age, in both the men and women This is almost wholly or wholly explained by the *cumulative* operation of both the blood lipoprotein and blood pressure factors over a period of years

Family History. That certain families are characterized by excessive rates of development of arteriosclerosis and a high incidence rate of coronary heart disease can readily be documented It has been shown in studies of a cross section of the population that a history of premature heart disease in the father is associated with an elevation in atherogenic index and, to a much lesser extent, with an elevation in the average diastolic blood pressure of the offspring These effects operate, not only in families with *extreme blood lipid* disorders, but also in those with more moderate ranges of blood lipoprotein levels

Overweight. The studies of Dublin and of Dauber show a higher incidence rate of coronary heart disease in overweight persons than in those of ideal, or less than ideal, weight Furthermore, pathological studies *show* a higher quantitative degree of coronary arteriosclerosis in overweight persons than in nonoverweight persons All these findings *are* quantitatively explainable by the combination of the effect of overweight in raising both the average value of the atherogenic index and the average blood pressure level No evidence has been brought forward to implicate the overweight per se as a mechanical-load factor in the explanation of these phenomena.

Diet. Dietary factors have been implicated, from a variety of sources of evidence, in the development of arteriosclerosis and clinical coronary heart disease Essentially all investigators in this area are convinced that dietary effects are primarily mediated by the effects of certain dietary constituents upon the levels of several lipoprotein classes Some suspicion exists that perhaps diet *may* also operate partly by an effect upon blood coagulability Diet can influence blood pressure levels as well

Two major classes of foodstuffs have been indicted for their effect upon blood lipid levels: (1) the *saturated animal and vegetable fats,* both of which can increase the S_f 0 to 12 and S_f 12 to 20 lipoprotein levels (and thereby the blood cholesterol level); and (2) *the carbohydrates,* which can increase the S_f 20 to 100 and S_f 100 to 400 lipoprotein levels (and thereby the total blood lipid level) It has been proved conclusively that these two dietary elements are the responsible agents, not the caloric intake they represent.

Cigarette Smoking. Hammond and Horn have conclusively shown that the incidence of clinical coronary heart disease is appreciably higher in regular *cigarette smokers than in* nonsmokers This effect is almost wholly or wholly explained by (1) an association of elevation of the atherogenic index with regular cigarette smoking; and (2) by the acute effect (during smoking) of cigarettes upon blood pressure levels There is no chronic, sustained effect of cigarette smoking on average blood pressure levels. The effect of cigarette smoking upon the serum lipoprotein level and atherogenic index appears reversible, since [illegible]

smoked. It is of interest that the studies of Hammond and Horn show that cigarette smokers who have ceased smoking regain part of the protection against coronary heart disease which characterizes nonsmokers Since *some* of the *accumulated* coronary arteriosclerosis is most likely irreversible, it is readily understood why former smokers do not regain *all* the protection possessed by nonsmokers, even though their lipoprotein levels revert to those of the latter.

Diabetes Mellitus. The quantitative increase in the incidence of coronary heart disease in diabetics as compared to the population at large and the relatively greater magnitude of this increase in the diabetic woman compared with the diabetic man are largely (and perhaps wholly) explained by the combined effects of average lipoprotein–atherogenic index elevation and blood pressure elevation in diabetics, contrasted with the population at large. In severe decontrol with acidosis, diabetic patients in general show massive elevations in the blood content of several lipoprotein classes

and of atherogenic index values, elevations which recede as acidosis and decontrol are corrected clinically. Even in the absence of clinical or chemical acidosis, it has been shown by Strisower et al. that strict chemical control of hyperglycemia and glycosuria through adequate use of insulin is, on the average, associated with lower atherogenic index values. These studies should help to resolve many emotional conflicts between the school of free diet management and the school favoring strict chemical control of diabetes.

Hypothyroidism. Severe *hypothyroidism* and *myxedema*, either spontaneous or iatrogenically induced, are characterized by marked elevation of the levels of S_f 0 to 12 and S_f 12 to 20 lipoproteins It is this elevation which accounts for the hypercholesterolemia of myxedema. In spite of claims to the contrary, there is every reason to consider the hyperlipoproteinemia (and hypercholesterolemia) of hypothyroidism to be an accelerating factor in the development of arteriosclerosis in the human being, just as would be the case in other situations where comparable elevation of blood lipid levels exists. Blumgart's contention (based upon a study of eight patients) that the hypercholesterolemia of myxedema is not an arteriosclerogenic influence has been refuted on the grounds that a number of cases ten to fifty times greater than that studied would be required even to test this concept.

Occupation. Morris' data indicate conclusively that certain occupations (in England) are characterized by incidence rates of coronary heart disease grossly higher than those for other occupations. In the main, his findings indicate that the physical activity associated with certain occupations seems to operate as a protective influence against coronary heart disease. A recent study of lipoprotein levels and blood pressure levels in 29 occupational categories of one industry has shown that there are large differences in lipoprotein–atherogenic index values between occupational categories.

Occupations involving heavy labor, such as performed by custodians and laborers, show the lowest atherogenic index values. This is consistent with Morris' contention. However, in certain occupational-group comparisons, the association of lipoprotein–atherogenic index values with the physical activity of the occupation does not appear to exist. In general, no appreciable relationship of occupational category to blood pressure level could be demonstrated; nor did responsibility, demands, and income level appear to be factors involved in determining blood-lipoprotein levels

Stress. With little in the way of quantitative measurement, a great deal of emphasis has recently been placed upon the "stresses of modern living" as a major factor determining the incidence rate of coronary heart disease Since such studies as have been reported have generally focused largely upon possible relationships of stress to blood lipid levels, the implication is a relationship of stress to development of coronary arteriosclerosis Unfortunately, no reported studies have adequately accounted for alterations in diet during periods of so-called excessive stress. In one study of accountants, a very slight (and not provably significant) elevation in mean serum cholesterol level was reported for periods of "maximal stress" versus periods of "maximal respite from stress." The very meager dietary data reported in that study indicate that what little effect (upon the serum cholesterol level) was observed could easily be accounted for by the dietary differences between the "stress" and "respite-from-stress" periods.

SUMMARY

Focal factors, little understood, do operate to determine the rate of progression of arteriosclerosis in various parts of the arterial tree The existence of focal influences is completely consistent with the existence of powerful general metabolic influences that determine the rate of development of arteriosclerosis Only *two independent general factors* have been shown to influence the rate of progression of arteriosclerosis. These are *the habitual level of certain blood lipoproteins* and *the habitual level of blood pressure.*

5

Aortic thrombosis and embolism

ELWYN EVANS

ACUTE THROMBOSIS

Etiology and Pathogenesis. Sénac (1749), according to Askey (1957), described the essential points of the current concepts of thrombosis generally credited to Virchow (1850). Both Sénac and Virchow described a triad of underlying thrombotic factors. the stimulus of damaged endothelium, the coagulability of the blood, and the degree and duration of stagnation of blood flow.

Thrombosis occurs where the endothelium is damaged by trauma, inflammation, atherosclerotic degeneration, or, *secondarily, as the* result of stasis of blood flow In the presence of *endothelial injury*, stasis increases the tendency to thrombosis by allowing more time for the interaction of thromboplastin and the other thrombotic components liberated at the *site of* injury

Because aortic thrombosis usually develops on degenerative *atheromatous lesions which* most commonly occur in the later decades of *life*, thrombotic occlusion predominantly affects the older age group Patients *in the* thromboarteriosclerotic group are on the average about 20 *years* older than those in the embolic group The ratio of males to females is about five to one.

Atherosclerosis of the aorta characteristically is most pronounced in the abdominal aorta, especially the distal portion; therefore, occlusive thromboses tend *to occur in the* narrowed lumen at or near the aortic bifurcation.

Symptoms. The symptomatology varies with the degree of preexisting stenosis *or narrowing* of the aorta (Pratt, 1954)

If sudden thrombosis occurs on an ulcerated atherosclerotic plaque, and the aortic lumen is almost normal, symptoms will be similar to those of an embolus at the aortic bifurcation. The important symptoms are almost entirely confined to the lower extremities, although, on rare occasions, a rapidly ascending occlusion will involve the mesenteric, renal, and other vessels with the appropriate *symptoms attending*. Symptoms predominantly consist of pain, anesthesia, and paralysis *Pain* occurs in about *four-fifths of the* cases, and at times radiates to the girdle or inguinal regions of the lower back. The pain varies in intensity, and is often described as excruciating, sharp, stabbing, dull, or aching (Reich, 1949). Loss of sensation *may* occur. Occasionally sensations are increased early, but later they are absent. *Weakness of the extremities* varies from slight weakness to complete paralysis and even *paraplegia*.

If a high degree of obstruction has developed slowly before acute thrombosis occurs, collateral circulation has had time to develop and ameliorate the symptoms of the acute occlusion

Signs. Signs also vary with the degree of preexisting aortic narrowing and collateral circulation *Absence of pulses is the outstanding* finding, but color and temperature changes are almost always *present*. The extremity may be black, cyanotic, mottled, pale, or white. It may be cold or clammy Reflexes may be abolished. *Varying degrees of shock* are usually present

Diagnosis. Occlusion of the abdominal aorta should be suspected when there is a sudden

onset of pain in the lower extremities and pelvis, especially when it is associated with temperature and color changes, sensory disturbances, weakness of the extremities, or paralysis. Disappearance of pulses in the femoral vessels and those below is the most important physical finding. Occasionally, the patient may go into shock or coma and expire before diagnostic signs or symptoms have had time to appear.

Acute aortic thrombosis must be differentiated from paraplegia due to other causes: poliomyelitis, transverse myelitis, peripheral neuritis, acute intraabdominal emergencies, cerebral vascular accidents, and especially embolism of the aortic bifurcation. The latter diagnosis depends primarily upon the presence of cardiac lesions which could be the source of emboli.

Prognosis. When acute thrombotic occlusions occur on ulcerated atherosclerotic plaques associated with almost normal aortic lumens, life expectancy without operation is similar to that in embolic occlusion. Often the course of acute thrombotic occlusion is milder than that of embolism because of variable degrees of preexisting stenosis and collateral circulation. The occlusion may become stabilized without loss of viability of the tissues of the extremity, then chronic arterial insufficiency develops Subsequently, development of collateral circulation may cause some gradual improvement and the appearance of the Leriche syndrome to be described later

Treatment. *Resection* of the occluded area and *grafting* should be considered in all cases. This should be done immediately if tissue necrosis or nerve damage appears evident but, if the condition appears to be mild, operation may be delayed to allow stabilization and more accurate diagnosis. DeBakey states that homografts are now obsolete, and that Dacron grafts should be used exclusively for all vessels

Caudal anesthesia or *antispasmodic drugs* may be used to help relieve vascular spasm.

CHRONIC THROMBOSIS

Several terms have been used to describe this condition including *insidious thrombosis* of the aorta and *the Leriche syndrome*. This syndrome is much more common than acute aortic thrombosis and is being recognized with increasing frequency.

Cause and Pathogenesis. As stated previously, aortic thrombosis is usually the result of thrombus formation superimposed upon atherosclerosis, and therefore is found with increasing frequency in older persons. However, chronic thrombosis of the terminal aorta at or near the bifurcation may occur in relatively young individuals. It may occur in either sex, but occurs most commonly in males between the ages of 40 and 60 years. In 24 cases operated upon by DeBakey et al. (1955c), ages ranged from 33 to 63 years, with an average age of 49 years.

Symptoms. Leriche (1923, 1940) and Leriche and Morel (1948) stated that patients, usually young men with irrelevant past histories, complained primarily either of inability to maintain a stable penile erection or of extreme fatigue of both lower extremities, instead of the well-known *intermittent claudication, extreme weariness* which came on quickly with walking and even standing, was reported.

Kirklin et al (1955) stated that partial or complete occlusion of the distal part of the aorta is characterized clinically by *distress produced by walking* and relieved by standing. Characteristically, the distress involves the thighs, regions lateral to the hips, buttocks, or rarely, the distal part of the midlumbar zone The onset is hastened when the patient walks rapidly or climbs an incline or stairs. It differs from the usual intermittent claudication involving the legs in that its location is more proximal. In rare instances, similar distress is produced by standing or exertion while standing, such as making beds or scooping grain.

Symptoms are frequently insidious in onset, but often incapacitating. Seventy-four patients with occlusion of the terminal aorta or iliac arteries were reviewed by Welch et al. (1957); of these, all complained of slowly *progressive distress* in the calf, thigh, hip, or back, induced by activity and relieved by rest This distress was described as a pain or a sensation of fatigue identical to claudication

Signs. Leriche (1923) described ischemic *pallor*, and emphasized global *atrophy* of the lower extremities without trophic lesions of

exposed parts of the skin and absence of pulses

Leriche and Morel (1948) described progressive changes extending 5 to 10 years or more: these included muscular atrophy, edema, absence of pulsation in the iliac vessels, pallor of the legs when standing and livid mottling when elevated, purplish discoloration, ecchymosis and ulcers over pressure points, and gangrene as a late manifestation. The atrophy is difficult to evaluate because a normal limb is not present for comparison.

Pataro et al. (1954) described 24 cases of aortoiliac thrombosis, in these there were marked coldness (seventeen cases), ischemic pallor (fifteen), erythromelia (four), cyanosis (six), dependent edema (one), distal lividity (one), and gangrene on the anterior part of the foot (one)

Of 47 patients with intermittent claudication of the hip and the syndrome of chronic aortoiliac thrombosis, 34 had good *extremity nutrition* and 8 fair nutrition (de Wolfe et al, 1954). Only five had poor extremity nutrition or definite trophic changes. It is of interest that three of these five patients had occlusion of the external iliac artery, *and that the other* two had involvement of the peripheral *arteries in* the lower extremities None of the patients with occlusion of the aorta or common iliac arteries had *only poor extremity nutrition*. The higher or more proximal occlusions are more likely to be associated with an adequate collateral circulation

The classic *sign is the diminution or absence of pulses in the lower extremities, and absence* of the femoral pulse is the most *important single* finding. Coelho et al (1955) *occasionally* found weak and easily *compressible* pulses in the inguinal region or below, *despite* complete aortic occlusion, these *pulses existed* because extensive collateral circulation had been established

Massarelli and Estes (1957) found the femoral artery pulse was absent in 39 *patients* and significantly *reduced in 66* Venous filling time in dependency, after *elevation of the feet*, was determined *in* 76 of their patients This was *found to* be normal in 25 patients and prolonged in 51.

Beckwith et al. (1958) *found a fairly* good correlation between the *intensity of the femoral* pulse, as determined by palpation, and the degree of occlusion above Poupart's ligament, as indicated by either aortography or gross pathological examination. *However, an absent femoral pulse did not indicate complete occlusion in all cases* Because of adequate collateral circulation, the pulses of the posterior tibial or the dorsalis pedis arteries were occasionally observed in patients with absent *femoral pulses.*

Massarelli and Estes described *bruits* over the abdominal aorta or iliac or femoral arteries in 12 cases in which they were mentioned. Beckwith et al. noted a bruit in the umbilical region or over the femoral arteries in 21 per cent of 65 cases.

Technical Studies. ROENTGENOGRAPHY. Plain x-ray films are not very helpful. Calcification of the aorta or pelvic vessels was noted in only 19 of 45 patients studied roentgenographically by de Wolfe et al (1954). When calcification was present, it was merely *confirmatory, and did* not necessarily correspond to the site of occlusion shown by aortography. Massarelli and Estes (1957) found evidence of calcification of the abdominal aorta in 37 of 105 patients, in several of whom it was discovered on reexamination of the films after negative roentgenographic reports.

OSCILLOMETRY. Oscillometric pulsations are *usually absent in the lower extremities*, but *may be detectable* in the thigh, despite absent *femoral pulsations*, because *of large collateral vessels*

AORTOGRAPHY Translumbar aortography, *introduced by dos Santos et al. (1929)*, fell into *disrepute in the United* States because of *permanent* vascular damage and death seen in experimental studies on dogs. The procedure *was revived* after extensive clinical *studies in urology* by Nelson (1942) and *Doss* (1942). Price and Wagner (1947) *first reported* its use in the diagnosis of aortic thrombosis. In recent *years*, the development of vascular *surgery* has been a *great impetus* for its widespread use.

Although *aortograms* have been widely used *in many medical* centers without serious ill effects, a *few authors* have *reported* abandoning its use because of *the* occasional reported *fatalities* and few *serious reactions* such as *paraplegia. Grossman* and Kirtley (1958) stated that they *had* abandoned its use, and that, *in cases suggestive of occlusive disease* of the aorta, surgical exposure and direct examination of the aorta and *its branches* was the optimal method of examination at this

time. Crawford et al. (1957) did not think aortography was necessary for diagnosis of complete obstruction of the abdominal aorta in those patients whose general condition prohibited surgery, but stated that it was of value in the diagnosis of incomplete obstruction and in the planning of surgery for this lesion Ellis and Kirklin (1956) stated that, although diagnosis usually could be made on the basis of clinical findings, aortography was an invaluable diagnostic aid in determining the site and extent of obstructions, delineating collateral circulation, and determining the patency of distal vessels.

Translumbar aortography, however, has been used in numerous cases (de Wolfe et al., 1954; Ellis and Kirklin, 1956) without mention of a serious reaction. Bahnson (1956) stated he used it in all of his cases but did not comment on complications. DeBakey (1958) stated that no complications had occurred in 300 cases examined since the precautions below, recommended by Crawford et al (1957), were followed.

1 Use aortography only when necessary.

2 Do not use it in complete aortic occlusion.

3. Limit the volume of injection to 15 to 25 ml of Urokon.

4. Use low concentration of the dye (70 per cent), and insert the needle below the renal arteries

According to Koszewski et al (1958), aortography is contraindicated in renal failure, and a blood urea-nitrogen content of 40 mg/100 ml is the limit above which aortography should not be attempted. It probably should not be done when there is a history of allergy. Koszewski et al. routinely administer *cortisone prior to examination.*

Occasionally, *femoral arteriograms* are also used to determine the extent of iliac thrombosis and the degree of arteriosclerosis of the major arteries in the legs. Rather than performing femoral arteriography, Ellis and Kirklin (1956) believe it is wise to explore the femoral arteries if aortograms fail to reveal patent vessels distal to the obstruction on delayed films and femoral pulsations are absent

Diagnosis. Despite the fact that diagnosis can usually be made on the basis of clinical findings alone, many patients are first seen by orthopedists or neurosurgeons. Because the syndrome of terminal insidious thrombosis of the aorta and iliac arteries is not widely known, the correct diagnosis often is not made, and a mistaken diagnosis is common.

Thrombosis of the aortic bifurcation should be suspected in patients complaining of easy fatigability of the legs, impotence, and pain in the lower back or abdomen, buttocks, hips, or thighs. The pain characteristically is brought on by exercise, especially walking, and relieved quickly by rest. Diagnosis is confirmed by absent or weak femoral pulsations. *A murmur may be heard over the groin when stenosis is present or collateral vessels are enlarged* Although aortography is not indispensable, many consider it important in confirming the diagnosis and determining the location and extent of the obstruction.

Massarelli and Estes (1957) stated that the diagnosis of aortoiliac occlusion was made clinically in 105 patients with intermittent claudication and bilaterally reduced or absent femoral pulses. This diagnosis was proved by aortography in eight cases and by necropsy in three.

Neither embolism nor acute thrombosis is usually mistaken for this syndrome. Most of the 47 patients reported by de Wolfe et al. (1954) were undiagnosed before admission; and many were referred as orthopedic problems with diagnoses such as ruptured intervertebral disks, osteoarthritis of the lumbosacral spine or hip, or bursitis of the hip. Differentiation is not difficult if one remembers to check the status of the arterial circulation of the legs of every patient who complains of pain in the lower back, hip, thigh, and leg Then, a carefully taken history will enable one to decide whether or not there *is true* intermittent claudication which can be caused only by reduced vascular supply to the musculature

Hypertrophic arthritis as a cause of hip pain is common after the age of fifty. The pain may be exaggerated by activity and relieved by rest, but the rest must be prolonged Some restriction of movement accompanies the pain, and roentgenograms may reveal typical cystic and sclerotic changes involving the acetabulum and the head of the femur.

Nonsuppurative bursitis or localized fibrosis are the most common causes of hip pain before the age of fifty. In bursitis, there is pronounced

tenderness over the bursa, and passive movements of the hip will usually aggravate the pain. In fibrosis, there are "trigger points" or areas of extreme tenderness in the muscle bellies or tendinous attachments of the muscles, and local infiltration of these tender areas with Novocain will usually give immediate relief.

Any pressure on, or irritation of, the fifth lumbar or first sacral nerve roots may cause pain in the posterior hip region and radiating down the course of the sciatic nerve. A protruding disk is not dependent upon movement for pain production, and the pain is almost always aggravated by bending, lifting, coughing, or straining. A protruded disk usually produces some change in the deep tendon reflexes of the involved extremity, and may cause characteristic sensory changes and muscular weakness in the leg.

Prognosis. Massarelli and Estes (1957) reviewed the natural history of 105 patients considered to have aortoiliac occlusion, the review covered survival rate, cause of death, development of ischemic changes in the lower extremities, severity of ischemic symptoms in surviving patients, and incidence of atherosclerosis elsewhere in the body

Survival rates for a period of 8 years after the time of diagnosis are somewhat less favorable than for those of a comparable normal population (Mayo Clinic). Thirty-six of the 105 patients were known to have died. Twenty-five (69.5 per cent) of these died as the direct result of atherosclerosis of the coronary or cerebral arteries. Five other patients presumably died as the result of atherosclerosis (two with congestive heart failure, one with rupture of a thoracic aneurysm, and two with generalized atherosclerosis). Thus, probably 30 of the 36 deaths were due to atherosclerosis elsewhere. None were known to have died from aortoiliac occlusion. Thirteen patients had some peripheral ischemic change other than claudication. Four had amputations as the result of peripheral atherosclerosis. Minor trophic changes of the toes occurred in three patients. Two diabetic patients had ulcers on their feet. Fifty-seven patients were followed for a minimum of two full years with respect to claudication. It was unchanged in severity from the time of diagnosis in 33, somewhat improved in 12, and increased in only 8.

The 3-year survival rate for patients with evidence of coronary or cerebral atherosclerosis, or both, at the time of diagnosis, was 60.0 per cent, as compared with 83.1 per cent for patients without such evidence. Although occlusion of one or both renal arteries has been reported elsewhere, renal-artery occlusion did not occur in the 105 patients reviewed.

During a 6-year study of 65 cases by Beckwith et al. (1958), 22 patients died while under observation. The duration of life from the onset of symptoms varied from 1 to 20 years, with a mean duration of 6 to 7 years. Death was usually due to disease of the coronary, renal, or cerebral arteries. The aortic thrombus extended cephalad to involve the renal arteries in only two cases.

Aortoiliac resection and grafting has an operative mortality rate of 4 to 5 per cent, and may relieve the high-level claudication, but obviously will have no effect on the cerebral, coronary, or peripheral atherosclerosis.

Treatment. Sufficient data are not available for adequate comparison of patients treated by resection and graft replacement and those treated conservatively.

Conservative treatment consists of bilateral lumbar sympathectomy, reflex heat to the abdomen for 20 min or more daily, elevation of the head of the bed 4 to 6 in., and instruction concerning the care of the feet. Smoking is forbidden.

Most authors now consider sympathectomy inadequate, however, Grimson et al. (1955) stated that excision of the lower thoracic and all of the lumbar ganglia gave encouraging results in the treatment of 19 patients who had unilateral or bilateral obstruction of the iliac arteries and the terminal aorta and viable limbs. There was no operative mortality, and only one limb required amputation—4 years after sympathectomy. These authors stated that results of this procedure were evaluated best by the satisfaction of the patient and warmth of the limb, and poorest by relief from claudication or improvement in oscillometric readings.

Leriche (1923) suggested that the ideal treatment would be resection of the occluded aortic segment with suture closure of the divided ends, and was the first to perform a terminal aortectomy together with a bilateral ganglionectomy (Leriche, 1940). Later Leriche and Morel (1948) emphasized the use of high bilateral lumbar ganglionectomy with resection of the thrombosed segment.

Thromboendarterectomy for aortic or iliac

obstruction was first reported by dos Santos (1947). Because *thrombosis tends to recur*, this operation has been discarded by *most* surgeons, although some *consider it satisfactory* for patients with a *short area of obstruction*.

At present, *excision of the involved area* and *grafting* are generally considered the procedures of choice. *The procedure is relatively simple, and good results can be expected if* distal vessels *are patent. If the* vessels are not patent distally, *the chances of getting into difficulty* with impaired circulation to the leg after operation are *considerable*.

Dubost et al. (1952) were the first to *resect a* portion of the abdominal aorta and use a *graft replacement*, but this was for an aortic *aneurysm*. *DeBakey et al (1955c)* reported their experiences *with 68* patients who had thromboobliterative *disease of the* abdominal aorta, in 64 of these excision of *the terminal* aorta and bifurcation together with *replacement* by *homograft were* performed There were only two *operative deaths* Three patients died later: one from *heart failure*, one from septicemia, and one from *hemorrhage* caused by rupture of the iliac artery *at the line* of anastomosis. All but four of the remaining 63 *patients* showed definite improvement Follow-*up studies* extending *2 to 5 years* revealed *maintenance of the good immediate* postoperative results. Bahnson *(1956) reported* good results on 14 and fair results on *patients on* whom excision and aortic reconstruction with *homografts* were performed. Ellis and Kirklin *(1956)* reported *two deaths*, a mortality rate of 4 per cent, in a group *of 47* patients undergoing resection and *grafting* for occlusion of the aorta or iliac arteries *or both* Forty patients (85 *per cent*) were improved, and the authors considered *these* results *eminently* satisfactory

Beckwith et al. (1958) reported a *series of eight* selected patients who underwent *resection and* homograft replacement There was one *hospital* death, and seven patients were distinctly *benefited* Patients considered suitable were *those with* minimal atherosclerotic involvement *elsewhere*, including the distal vessels, however, suitable patients were rare because of the usual *associated* generalized atherosclerosis.

Massarelli and Estes (1957) described the "ideal" candidate for surgery, recognizing that the primary aim was relief of claudication. *The* candidate should have "*sufficiently severe* claudication" to warrant both the *mortality* and morbidity risk and the expense and inconvenience of surgical treatment. Preferably, the *candidate should* have no clinical evidence of *coronary* or cerebral atherosclerosis, no diabetes mellitus, and no other significant systemic disease. Then, if the femoral arteries are patent, he may be considered an ideal candidate for aortic resection and graft.

At present, experience with *synthetic aortic substitutes* is encouraging, but the durability of these materials under biologic conditions has not yet been fully determined The most satisfactory materials to date appear to be Dacron *and Teflon.* DeBakey (1958) is now using Dacron exclusively for all grafts.

EMBOLISM

Causative Factors. Over 90 *per* cent of the cases of systemic arterial embolism arise from thrombi in the left atrium or ventricle.

Haimovici (1950) reviewed 230 unselected cases of peripheral arterial embolism and found *that* 51 per cent were associated with *coronary heart disease* and that 44.4 per cent were associated with *rheumatic heart disease.* Flasher and Stephenson (1952) reviewed 212 cases and found 145 cases (69 per cent) to be of atrial origin, and only 50 (23 per cent) to be of ventricular origin.

Although bacterial endocarditis causes about 5 per cent of systemic arterial emboli, they are of no significance in embolism of the aortic bifurcation because of their small size. Other, rarer, causes are paradoxical emboli from systemic veins or the right side of the heart and emboli from thrombi in the pulmonary veins *or* in aortic aneurysms.

In rheumatic heart disease, most left atrial thrombi occur in cases with *predominant mitral stenosis* They occur less frequently when regurgitation is superimposed upon stenosis, and still less frequently when regurgitation is present alone (Storer et al, 1954). However, *atrial fibrillation* is the main correlate regardless of the mitral lesion (Askey, 1957). Harvey and Levine (1930), after reviewing 111 cases of uninfected atrial thrombosis, concluded that atrial fibrillation undoubtedly increased the incidence of atrial thrombosis. Prinzmetal et al. (1952) stated that it was not the fibrillation itself but the concurrent stasis caused by mitral obstruction that predisposed to the thrombosis. Atrial fibrillation occurs not only at a later age but also later in the course of mitral *disease. It* occurs more frequently in pure mitral regurgitation than in pure *mitral stenosis* (Storer

et al., 1954; Janton et al., 1954) and indicates prolonged stasis in cases of pure stenosis with minimal but moderate regurgitation, and prolonged but minimal stasis in cases of pure regurgitation

Increased blood coagulability may contribute to thrombosis in the older patients.

By compiling data from 450 cases of rheumatic heart disease with clinically recognizable systemic arterial embolism (presumptive evidence of left atrial thrombosis), Askey (1957) found that emboli were most frequent in patients *without* congestive failure, indicating that thrombi usually form *before* the onset of congestive failure. Daley et al. (1951) were unable to correlate the duration and severity of failure with systemic arterial emboli. Enlargement of the mitral orifice by commissurotomy is occasionally followed by an embolus large enough to obstruct the aortic bifurcation

In left ventricular (*mural*) *thrombosis*, the thrombotic tendency of the *endothelium* with damage secondary to myocardial *infarction* is much greater than in rheumatic fever. This strong thrombotic tendency is exaggerated by stasis, which is increased by congestive heart failure The greater incidence of thrombi in infarcts of the anterior wall is probably caused by increased stasis at the apex, especially in congestive failure (Jordon et al, 1952) The incidence of thrombi is less in healed *infarctions*

Thus, prolonged *stasis* is needed for thrombus formation in the left atrium. In atrial thrombosis, atrial fibrillation is an important correlate while heart failure is not. Endothelial damage is the most important factor in thrombosis of the left ventricle Here, atrial fibrillation is not a correlate, but heart failure definitely is.

Daley et al (1951) analyzed 393 cases of systemic arterial embolism and found that 23 (5 9 per cent) had lodged *at the bifurcation of the aorta* Haimovici (1950) stated that, in 330 cases of arterial embolism, 9 1 per cent had lodged there

In general, the factors which tend to dislodge thrombi from cardiac cavities are also those which tend to prevent their formation In most instances, however, there is no satisfactory explanation for the mobilization of left atrial thrombi, although occasionally there appears to be a definite relation to a sudden change in cardiac rhythm (Askey, 1957) Of special significance in aortic embolism is the fact that the mitral orifice must be small enough to cause the necessary stasis for clot formation, but sufficiently large to permit the passage of an embolus large enough to obstruct the aortic lumen. A change in the contractions of the ventricular wall probably is the most important factor in the dislodgment of left ventricular mural thrombi.

When the emboli become lodged, a local reaction of *edema* starts in the intima, and the force of blood behind the embolus increases the pressure on the intimal wall accelerating the reaction (Pratt, 1954). *Arterial spasm* probably always occurs, affecting the collateral circulation as well as the involved vessels. Hesse (1921) stated that vasospasm occurred in 97 per cent of the cases of saddle embolism, especially distally. In fact, total occlusion of the lumen by the embolus is not essential Partial block may be converted to complete block by vasospasm and subsequent secondary thrombosis (Reich, 1949). In more than *one-half* of the patients, a soft clot is propagated distally

Symptoms. The most dramatic clinical picture of sudden arterial occlusion occurs when *the abdominal aorta is occluded at its bifurcation* (*saddle embolus*) (Allen et al, 1955).

There is usually a history or symptoms of heart disease

The presenting symptom is usually *leg pain,* although it may be minor or absent in 15 to 20 per cent (Pratt, 1954) *Abdominal or sacral pain* may predominate. Of 27 cases, lower abdominal or sacral pain was recorded in 15 (Taylor, 1951).

Pain often decreases as other symptoms such as *paresthesia, anesthesia,* and *paralysis* become more marked. Occasionally, paresthesia and anesthesia overshadow pain. Paresthesia or anesthesia was recorded in 23 of Taylor's 27 cases, and paralysis of the lower extremities was present in more than one-half of the patients

Signs. Most of the patients with embolism of the aortic bifurcation appear *anxious* Signs of heart disease are often evident *Coldness of the skin, pallor,* or *cyanosis* are present. In more than one-half of Taylor's cases the skin of the legs was mottled, and in the rest the skin was recorded as being cyanotic or white. The marble-white appearance described in aortic thrombosis is not characteristic of embolic aortic occlusion. The appearance of the

skin seems to depend largely upon the amount of venous stasis or collateral blood supply, and is of no diagnostic value.

Anesthesia of the feet is complete. Paralysis involves the small muscles of the feet, and usually includes motor muscle groups to the ankle (Pratt, 1954).

Complete absence of pulsation of the femoral, popliteal, and more distal pulses is almost constant; occasionally, however, it is only diminished, the lessened pulsation being produced by pounding of the blood pressure against the occlusion or by transmission of the pulse through the fluid in the iliac system. Absence of pulsation of the aorta over the sacral promontory together with normal pulsations more craniad have been described.

Technical Study. Because of the importance of elucidating the source of the embolus, which arises from the left side of the heart in well over 90 per cent of the cases, roentgenographic and electrocardiographic studies of the heart are important

Roentgenography is most important in diagnosis of left atrial enlargement in mitral disease Sosman (1943) stated that fluoroscopy with optimal accommodation of the eyes is better than the roentgenogram in the diagnosis of calcification of the mitral valve, which he considers diagnostic if observed roentgenographically, regardless of the presence or absence of other signs.

Occasionally, the electrocardiogram is helpful The presence of notched P waves and a history of rheumatic fever suggest the probability of mitral stenosis. The electrocardiogram is, of course, the most valuable technical aid in the diagnosis of arteriosclerotic heart disease

Oscillometry is of limited value since the same information can be obtained by careful digital examination.

Diagnosis. The six "P's" of arterial occlusion which may aid in diagnosis are pain, paralysis, paleness, pulselessness, paresthesia, and prostration. The following triad may also be helpful in diagnosis· (1) sudden complete loss of pulse to the lower extremities with resulting ischemia; (2) presence of a heart lesion capable of casting off an embolus large enough to occlude the terminal aorta, (3) absence of history suggesting aortic thrombosis on an arteriosclerotic basis.

Signs and symptoms of sudden occlusion of the aortic bifurcation should cause one to suspect and look for heart disease, either coronary or rheumatic with mitral stenosis. When such signs or symptoms suddenly occur in patients with rheumatic or coronary heart disease, one should suspect aortic embolism. This is particularly true if mitral stenosis is accompanied by atrial fibrillation, or if coronary heart disease with myocardial infarction is accompanied by heart failure.

It is well to remember, however, that the onset of symptoms in embolic obstruction of the aortic bifurcation may not be sudden, that occasionally the episode may be silent, and that numbness or coldness may be the initial symptoms instead of pain.

Acute aortic thrombosis and acute phlebothrombosis with massive arterial spasm are the main differential diagnostic problems A primary point is the presence or absence of a source for emboli, particularly rheumatic mitral disease or coronary heart disease.

Although the onset of thrombosis at or near the bifurcation of the aorta is usually gradual, it may be sudden. If thrombosis is superimposed upon a high degree of stenosis which has developed slowly, the collateral circulation lessens the severity of the symptoms, and often there is a history of failing circulation in the legs. If thrombosis develops on an ulcerated atherosclerotic plaque and the aortic lumen is almost normal, peripheral symptoms and signs may be similar to those of an embolism at the aortic bifurcation. Heart disease does not necessarily accompany acute thrombosis

In thrombophlebitis with massive spasm of the corresponding artery, the symptoms and signs are unilateral. Initially, edema and cyanosis may be absent, and the corresponding femoral pulse may be temporarily absent After a few minutes to a few hours, edema and cyanosis appear, and the femoral pulse returns In phlebothrombosis, the leg is generally warmer than in embolism Paralysis and other differential points of embolism are important. If necessary, paravertebral blocks and antispasmodic drugs may help differentiate vasospasm.

Warren and Linton (1948) suggest that it is better to err on the side of embolism because therapy cannot wait upon academic proof

Concurrent venous thrombosis may occasion-

ally accompany embolism, and often occurs in cases terminating unfavorably.

Prognosis. The natural clinical course depends upon the degree of development of collateral circulation, the cardiac *status, and* the general condition of the patient. *Death or loss of limb occurs in a large proportion of patients with aortic embolism. When there is no surgical intervention, practically all patients die.* Successful *embolectomy* offers the only prophylaxis against impending gangrene, but does not alter the cardiac hazard. Successfully embolectomized patients may subsequently die of the severe cardiac disease which is the source of *the large aortic* embolus or of a subsequent fatal embolism. Because of this, the mortality rate is nearly as great with embolectomy as without it (Pratt, 1954, Dye et al., 1955)

In an analysis of 128 untreated or conservatively treated cases, Haimovici (1950) reported that 61 (47.6 per cent) died in the hospital. Of 67 patients discharged alive, 56 (43.8 per cent) had no follow-up, 6 (4.7 per cent) died in 6 to 24 months, and 5 (3.7 per cent) were alive with a follow-up of 2 to 10 years. The hospital mortality rate of surgically treated cases was 51.7 per cent which was slightly above that of the medically treated cases.

Reviewing his total series of 300 cases, Haimovici found that the proportion of marked ischemia and early deaths was about the same in patients not treated, in those treated late or poorly (heat on or elevation of extremities), and in those treated properly and early (*within 12 hr*), *and* varied from 11.3 per cent in the first group to 14.4 per cent in the last. Late or poor treatment *increased the incidence of gangrene from 28* per cent in the untreated cases to 35.3 per cent, early and proper conservative treatment decreased the *incidence of gangrene* to 14.4 per cent. Poor or late treatment increased the incidence of chronic postembolic ischemia, and decreased the incidence of nonischemic limbs.

Most authors agree that survival of the limbs is greater, and that gangrene and ischemic pain of the extremities are less, when *embolectomy* is performed. Favorable local results depend upon early treatment, the condition of the endothelium following surgery, and the state of the distal arteries before embolectomy. Embolectomies have been more frequently successful since the advent of *anticoagulants*.

In rheumatic heart disease, the danger of future embolism is statistically much greater after the first attack. Once a thrombus is formed in the left atrium and has been mobilized, the underlying background for recurrent embolism persists and, until this is altered, the frequency of recurrent emboli will remain unchanged.

In a series of 60 "successful cases" following embolectomies of all types, one-fourth died from recurrent embolism within 1 year, one-half in 3 years, and two-thirds in 5 years. *Hemiplegia* occurred in 12 of the 41 patients who died and in 4 of the 19 survivors (Strombeck, 1935). *About* half of the rheumatic fever patients who recovered from a first embolus of any type eventually died of recurrent arterial embolism (Askey, 1957). Of 201 *recurrent* episodes of embolism in rheumatic heart disease, 144 (71 per cent) *occurred* within the first year. Of these, as many occurred within the first month as within the last 11 months, and of these, as many occurred in the first week as within the next 3 weeks (Daley et al., 1951).

Prognosis, especially in the rheumatic fever group, has strikingly improved since the advent of anticoagulants and cardiac surgery. Wright and Foley (1947) first showed that recurrent embolism in rheumatic heart disease could be reduced by continuous *Dicumarol* therapy. Summarizing five reports on 98 patients followed for 1,944 months without Dicumarol before the first recognizable embolism, and for 2,995 months with Dicumarol after embolism, Askey found that the incidence of embolisms was reduced from 1 in 7 months to 1 in 7 years.

The occurrence of emboli after mitral valvuloplasty is almost nil. Glover et al (1954) stated that, in a postoperative experience covering 6 years, only one questionable and minor embolic episode occurred in 700 patients. Bland et al (1954) reported that only one possible small cerebral embolism occurred during 70 months following valvuloplasty performed on seven patients who had had 30 embolisms in 372 months preceding surgery. Crane (1958) reported results of embolectomy on 14 patients, 12 with mitral stenosis and 2 with recent myocardial *infarction*. Ten of the twelve rheumatic patients survived. Eight of the ten did well, and two required low-thigh amputation. Mitral valve *surgery* was performed on eight of the ten living *patients, four* shortly before embolectomy and four afterwards.

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Labey (1911) performed the first successful embolectomy, but Bauer (1913), using a midline transperitoneal exposure, is given credit for the first successful removal of an aortic embolus. Nystrom (1936) developed the "retroperitoneal Hinuntermelkung" procedure which consisted of introducing one hand beneath the inguinal ligament and behind the peritoneum until the embolus could be outlined by palpation The embolus then was milked downward by the exploring fingers until it could be removed through an iliac or femoral artery incision.

Murray (1943) reported the first group of successful cases of aortic embolectomy, however, isolated successful cases had been previously reported Warren et al (1954) reported a series of 17 cases, of which seven survived with preservation of both limbs, and one with one limb

At present, most authors prefer to use the direct exposure of the bifurcation of the aorta, either by the transperitoneal or the extraperitoneal approach

Most authors consider *heparin* administration important in the preoperative and postoperative periods Crane (1958) states that the decision whether or not to use heparin postoperatively should be weighed in each case. Heparinization may cause major blood loss after retroperitoneal dissection Therefore, if it is used, hematocrit determinations should be made twice daily.

In seriously ill patients, aspiration of the embolus from below the inguinal ligament through the common femoral artery on both sides may be attempted under local anesthesia. If this fails, the direct approach is necessary.

If patients are eligible for mitral valvuloplasty, this procedure should be considered before embolectomy or as soon as practical thereafter. *Mitral valvuloplasty* should be considered immediately after any arterial embolism because minor attacks often precede major ones Glenn and McNeill (1957) performed a successful emergency valvuloplasty before embolectomy in a patient who had hypotension and pulmonary edema and who did not respond to usual therapeutic measures They stated that, when signs of severe congestive heart failure are present, it appears reasonable to consider an *emergency valvulotomy and atrial appendectomy* before aortic embolectomy. In Crane's series (1958), four valvuloplasties were performed successfully before embolectomy, and four were performed successfully afterwards

The striking recent improvement in prognosis in the rheumatic group is presented well in the statements of two observers over the period of the last 7 years. In 1951, Taylor stated that "successful aortic embolectomy is so spectacular as to completely overshadow its true medical worth. It is fortunate that this procedure does not have to be considered in the light of its general medical benefit. Mankind would be far better served if the same time, effort, and money would be spent on some dull public health problem." In 1958, Crane stated that "with improved preoperative medical management of cardiac patients, greatly improved anesthetic techniques, monitoring of the heart during operation, the widespread betterment of vascular surgery in general, and the prevention of further emboli by cardiac surgery, the patient sustaining aortic embolism has a good outlook, provided diagnosis is prompt and early embolectomy done."

That recurrent embolism is a sequela of myocardial infarction is well known, but the incidence is less well established than in rheumatic heart disease. Although the outlook is grave in patients with aortic embolism and coronary heart disease with myocardial infarction, the consensus is that the incidence of thromboembolism is significantly reduced by the practice of continuous anticoagulant therapy.

Treatment. Prophylactic treatment primarily consists of (1) *anticoagulant therapy* in rheumatic heart disease with mitral stenosis after an initial embolism, in coronary heart disease after myocardial infarction, and in congestive failure (providing no contraindication exists); and (2) mitral valvuloplasty in eligible patients with mitral stenosis.

A most important step is the recognition of a minor embolism which usually precedes a large or fatal one.

Continuous anticoagulant therapy is indicated in eligible patients with mitral stenosis who are ineligible for or refuse valvuloplasty. Although any reduction in prothrombin activity reduces the incidence of thromboembolism to some extent, moderate reduction is sufficient for many patients. Askey (1957), after treating 304 patients with chronic cardiovascular disease for periods of 3 months to 9 years, concluded that 50 per cent reduction in prothrombin activity was satisfactory in ambulatory patients. The patient, of course, should be properly instructed concerning precautions and complications.

Contraindications to prolonged anticoagulant therapy are conditions which predispose to serious hemorrhage, inadequate laboratory facilities, inexperience of the physician, and the inability of the patient to cooperate for one reason or another.

Patients who are eligible for *mitral valvuloplasty* should, of course, be operated upon, and anticoagulant therapy should be maintained until surgery and, possibly, through surgery. Storm and Hansen (1955) maintained Dicumarol therapy through mitral valvuloplasty in 26 cases and found no more hemorrhage than they did in 26 control cases. None of the treated cases had thromboembolic complications, but four of the control cases had postoperative cerebral embolisms. It is important to check peripheral pulses before and after surgery because of the relative frequency of postoperative emboli.

Treatment of embolism of the aortic bifurcation may be conservative or surgical.

Conservative measures include anticoagulants, protective bandages for the limb, reflex hyperemia, vasodilator drugs, and paravertebral sympathetic block. Elevation of the extremities increases the ischemia, and the application of heat increases tissue metabolism, so they should not be used. Cooling slows down tissue metabolism, but increases vasospasm, and is not recommended.

Embolectomy is the method of choice and should be considered in every case, especially if conservative measures fail after 2 to 4 hr. Crane (1958) stated that embolectomy should be done as soon as practical for five reasons: "Signs of improvement in circulation are often transient, and valuable time is lost in wishful thinking, no one can tell with certainty whether or not an embarrassed limb will survive because of the constant hazard of added thrombosis in the blocked arterial tree; anticoagulant therapy is only partially effective in preventing clot propagation; no collateral flow can truly replace main channel flow; and late thrombectomy or thrombendarterectomy is more difficult to accomplish and much less rewarding than early embolectomy." *Complete restoration of the arterial lumen usually can be accomplished if embolectomy is performed within 6 to 10 hr,*

but it is desirable to intervene earlier if possible.

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Dissecting and mycotic aneurysms of the aorta

Pathological Aspects
IRA GORE
Clinical Aspects
WILLIAM H. WEHRMACHER

PATHOLOGICAL ASPECTS

DISSECTING ANEURYSMS

Dissecting aneurysm is the designation given to the vascular deformity which results from hemorrhage within the wall of an artery For practical purposes, it is a condition confined to the aorta; involvement of other channels rarely occurs Historically, Laënnec (1826) introduced the diagnostic term, however. Shennan has credited Nicholls (1761) with the first unmistakable description A century later (1863) Peacock was able to assemble 80 cases for review The clinical diagnosis of dissecting aneurysm dates from the case of Swaine and Latham (1856) As late as 1934, Shennan was able to find only six cases that had been recognized clinically, but since then, ante-mortem diagnosis has become commonplace

TABLE 15-1 EFFECT OF REENTRY ON THE PERIOD OF SURVIVAL

	Reentry	*No reentry*
Survival period:		
Less than 5 weeks	26 (28%)	192 (96%)
More than 5 weeks	66 (72%)	7 (4%)
Total	92	199

SOURCE: Morgan-Jones and Langley, 1946

There is evidence of an increasing frequency of aortic dissection and currently it comprises 12 to 25 per cent of all aortic aneurysms The incidence is greatest between the ages of 40 and 60 years, though no age group is exempt Men are twice as often affected as women, but this difference lessens after the age of sixty. Negroes seem more susceptible than Caucasians but by allowing for the greater frequency of hypertension among Negroes, Levinson et al. found no difference in the incidence of dissecting aneurysm

Dissecting aneurysm carries a very high mortality; most victims succumb within a short time but sudden deaths are uncommon. According to Hirst et al , 79 per cent live longer than 24 hr, 51 per cent more than 4 days, and 26 per cent longer than 2 weeks. DeBakey et al (1955b) have emphasized that prompt clinical diagnosis allows adequate time for surgical intervention In a minority of cases, survival may be prolonged. Sixteen of 300 cases collected by Shennan lived longer than 1 year, Morgan-Jones and Langley (1946) described an instance of 30-year survival External rupture of the aneurysm and hemorrhage causes death in the great majority of acute cases Bleeding occurs into the pericardium in 75 per cent of cases; other sites in order of frequency are the pleural cavities, the medi-

astinum, and the retroperitoneal space. Internal rupture or reentry improves the possibility of prolonged survival by reducing the incidence of hemorrhage. The prognosis is also improved as the distance of the intimal tear from the aortic ring increases

Congestive heart failure and hemorrhage are the principal causes of death in chronic dissecting aneurysm. Hemorrhage results from rupture of the original lesion or from additional and even multiple independent episodes of dissection

Pathological Findings. Most of the gross features of dissecting aneurysm have been known for more than 100 years Elliotson observed in 1829 that the ascending aorta was the usual site of the lesion and that internal rupture (when present) was commonly transversely oriented. Independently, Pennock (1838) and Henderson (1843) recognized that dissection occurred within the media, Henderson even localized it more precisely to *the outer portion* of that layer. As shown in Table 15-2, the initial intimal tear may involve other portions of the aorta.

The external deformity of the aorta results from the intramural hemorrhage and may be *saccular* or *fusiform* Often the natural lumen is narrowed by the inward bulge of the false channel. The longitudinal extent of dissection varies from a few millimeters, so-called "spontaneous rupture," to the length of the aorta, even more when it extends beyond the bifurcation (Figs 15-7 and 15-8). Cleavage usually extends distally but some degree of *retrograde* extension is common, particularly with prolonged survival. Seventy-six per cent of dissections originate *in the ascending aorta* Of this 76, 36 do not progress further than the arch and 40 extend into the thoracic and the abdominal aortas Sixteen per cent of dissecting aneurysms arise in the aortic arch and most of them progress to involve the abdominal aorta. Even more distal dissection is not uncommon; Gore and Seiwert found the vessels to the lower extremities to be involved in 19 of 85 cases Despite the involvement of the abdominal aorta in more than half of all dissections, the terminal hemorrhage is intrathoracic in the great majority. Even patients with older, canalized dissecting aneurysms frequently succumb to hem...

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TABLE 15-2. ANATOMIC SITE OF INTIMAL TEAR IN DISSECTING AORTIC ANEURYSMS

Location	Cases (per cent)
Ascending aorta	63
Transverse aortic arch	18
Distal aortic arch	10
Thoracic aorta	7
Abdominal aorta	2

Reference has already been made to the importance of reentry tears in favoring survival; however, absence of such a second tear does not preclude prolonged survival. As it progresses within the wall of the aorta, the dissecting hemorrhage may compress or intercept subsidiary channels. Almost invariably some of the numerous segmental arteries are involved (Fig. 15-7). These, it will be recalled, are the source of the spinal arteries; their attenuation before tearing seems to account for *transient* cord symptoms. Depending upon pressure relations, the ostiums of the intercepted channels may provide a route for reentry into the aorta, moreover, the distal extensions of these arteries now arise from the false channel and also serve to decompress it The longitudinal and circumferential extents of medial cleavage are variable but the process may affect the coronary arteries, the great vessels of the arch, the celiac axis, the superior and inferior mesenteric, or the renal arteries. Of the 22 cases cited by Burchell, ". . . the right and left coronary orifices were each involved twice, the innominate artery five times, the left carotid six times, the left subclavian eight times, the celiac axis and superior mesenteric each twice, the left renal artery nine times and the right twice, and the left iliac 12 times and the right nine times" Rarely, the medial hemorrhage may extend into and along the great vessels of the arch just as it does, more frequently, into the iliac arteries.

Much has been made of the transverse orientation so frequently observed in the primary intimal tear, it has been considered a clue to the mechanical factors involved in the develop-ment of ...

...sons under 40 years of age. For this reason, *mechanical influences must be regarded as only supplementary to more fundamental structural changes.* With chronicity, the intimal opening becomes endothelialized and



Fig. 15-7. Heart and aorta Dissecting aneurysm. The arrow indicates the intimal tear in the supravalvular segment of the aorta. In the thoracic aorta at the top of the photograph are the ostiums of the disrupted segmental vessels

rounded or ovoid, and simultaneously an endothelium forms in the false channel Prolonged survival even permits the development of appreciable atherosclerosis in the newly formed intima

Occasionally dissecting aneurysms occur *without* an intimal tear, this type was described by Krukenberg (1920) and Tyson (1931). Six of the 85 cases studied by Gore and Seiwert were of this variety The survey of Hirst et al. led them to conclude that similar instances comprise about 10 per cent of all dissecting aneurysms. However, their relative infrequency is no measure of their significance since they



Fig. 15-8. Dissecting aneurysm of the aorta, transection magnified about 2½ times The false channel at the top is occupied by a thrombus which compresses and narrows the natural lumen. At the right side of the photograph, it is apparent that the cleavage plane involves the outer portion of the media The aortic intima is eccentrically thickened by degenerating and hemorrhagic atheromatous plaques which have only a coincidental relation to the medial dissection.

demonstrate that *intimal tearing is not the primary event* in the genesis of intramural dissection

An even more uncommon lesion, which should be grouped with dissecting aneurysms, is the one known as *incomplete rupture of the aorta*. This lesion, well-illustrated by Peery (1942) and by Fisher and Salmons (1950), had been originally described by Eppinger (1887) as a healed rupture. As the name implies, there is a gaping, nonpenetrating rent in the intima and media which characteristically lies in the supravalvular segment of the aorta. Usually the tear is transversely oriented and may be bridged by a few tenuous strands. Survival allows endothelialization of the base of the tear and reinforcement of the aortic wall by adventitial scarring However, the prognosis should be guarded since there is invariably medial degeneration and the probability of subsequent intramural dissection and pericardial hemorrhage There is also the additional hazard of aortic insufficiency resulting from the proximity of the lesion to the valve ring

Pathogenetic Factors. The frequency of hypertension coincident with dissecting aneurysm is such that it has been regarded by some as the principal pathogenetic factor However, since the lesion appears in normotensive persons, particularly in the younger age groups, elevated blood pressure cannot be more than a secondary factor. Nor do transitory increases of arterial pressure appear important; trauma, state of activity, or exertion have no demonstrable relation to the onset of dissection

The normal aorta resists bursting or dissecting pressures far in excess of those observed in the most extreme [illegible] in [illegible] is [illegible] of serious weakening of the vessel wall Although earlier students had considered intimal disease to be the weakening process, the site of origin of most dissections is in the proximal aorta, the portion least affected by atherosclerosis It is true that intimal disease is well advanced in the older age groups in whom dissecting aneurysm is most frequent, but the lesion occurs in young individuals in the absence of appreciable atherosclerosis. Moreover, coincidence of a plaque and an intimal tear is uncommon. Gore and Seiwert noted it only twice in 85 cases and Shennan only six times in 218 cases. But while intimal disease is not an explanation for dissecting aneurysms, *structural weakening of the media* is, and this has been observed to such a degree that mere manipulation may demonstrate the defect. Microscopically, the distribution and frequency of medial lesions in the aortic wall correspond to the distribution of intimal tears in dissecting aneurysm They occur uniformly in young as well as in aged victims of the disease. Although the major structural weakenings may have been destroyed by the intramural hemorrhage, it is possible to find focal degenerative medial lesions in virtually all cases.

Microscopically the medial changes are of two varieties The first, described by Gsell (1928), is characterized by foci of medial-muscle depletion with no alteration in the elastic laminas except condensation. Cellina observed similar lesions in senescence. Intercellular accumulations of mucoid material occur, but are not as prominent as in the second type of medial degeneration, described by Erdheim In the latter form there are large gaps and faults in the elastic laminas, these are filled with excessive accumulations of mucoid ground substance; these compress and distort the surrounding medial tissues With depletion of the elastic lamina the muscle fibers, which insert upon them, retract and become malaligned, but are otherwise unaltered. In a series of 72 cases reviewed histologically, 36 presented damage to the muscular laminas, 16 were characterized by focal destruction of elastic tissue, and 20 presented lesions of mixed character The elastic-tissue type of degeneration proved to be the predominant form in younger individuals (40 years and under), whereas the muscular type of lesion was more prevalent in the older group. In routine autopsy material, lesser degrees of these structural changes are often observed. The presumption is that dissecting aneurysm is the exceptional occurrence which complicates severe forms of a fairly common process. As previously mentioned, these lesions have a predilection for the ascending aorta and arch and appear to be accentuated by hypertension

Reparative changes occur with either form of medial damage The "mucinous" accumulation which may be such a conspicuous component of the lesion is also quantitatively a

variable one and is therefore regarded as a reactive change. Its presence is entirely nonspecific since similar accumulations occur in arteries in response to a wide variety of irritative processes. The increase of ground substance is not entirely acellular. Gsell (1928) observed stellate cells sparsely distributed in the basophilic accumulation and stated that, in old lesions, fibrous tissue replaces the mucoid material and repairs the medial defect. In common with other reparative reactions, there is increased vascularization, a mild perivascular influx of inflammatory cells, and peripheral (adventitial) fibrosis These features, greatly intensified, may also be seen in rheumatic, rheumatoid, and syphilitic aortitis. However, none of them predisposes to dissecting aneurysm (Weiss, 1935) The relative indolence of the reparative reaction in idiopathic medial degeneration is the reason for its vulnerability to dissecting aneurysm The bland reaction characteristic of the idiopathic degenerative process fails to narrow the vasa, to support them with sheaths of inflammatory tissue, or to bridge the gaps in the media Instead, the thin-walled vessels lie essentially unsupported *in a focus of medial weakening*, a condition suggesting great vulnerability to rhexis. That this indeed occurs is evident from reports of isolated intramedial hemorrhage; this is the circumstance that explains occurrence of dissecting aneurysm without intimal tears (Fig. 15-9).

Once intramedial hemorrhage has occurred, the sequence of events would seem to depend upon the extent of the degenerative change The extravasation, compressed and propelled by the tension to which the aortic wall is subjected, exploits its weaknesses. Thin-walled vasa in its path are interrupted, and with expansion of the hemorrhage an ischemic component is added to the vascular lesion. Rapid and accelerated progression results from either rupture of the intima overlying the intramural hemorrhage, or the opening of large arterial channels intramurally, or both Since there may be some question as to the possibility of hemorrhage into a structure which is continually under tension, it should be noted that the pulse wave in the vasa vasorum arrives *after* the main aortic pulse has passed. It is this asynchronism which permits them to function against the tension of the aortic wall. Hypertension would clearly increase the possibility

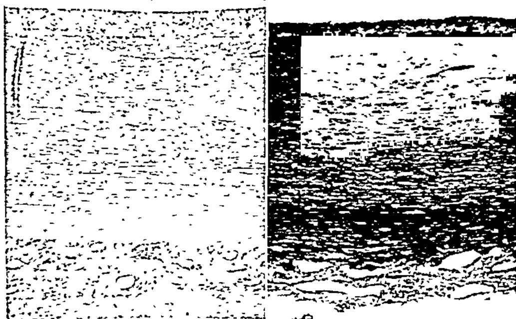


Fig 15-9. Aortic wall disclosing an organized and healed dissection tract in the outer portion of the media The defect is more obvious with the elastic tissue stain to the right. On the luminal side of the lesion, observe the condensation of elastic fibers and the relative pallor of the analogous portion to the left, an index of the depletion of muscle fibers. ×40.

of rhexis and would, in part, explain the high incidence of dissecting aneurysms in hypertensive individuals Nonetheless, it is clear that elevated arterial tension is merely a secondary factor in the pathogenesis of dissecting aneurysm

Etiologic Considerations. Although the cause of medial degeneration is unknown, a number of suggestive correlations may be noted. *Congenital anomalies* involving the vascular system, such as coarctation of the aorta, bicuspid aortic valve, and arachnodactyly, are found to be associated with an unusually high incidence of dissecting aneurysms suggesting that there may also be some congenital disturbance involving the vessel wall Indeed, Wolff (1932) and Holle (1947) reported medial elastic-tissue defects as the explanation for aortic aneurysms occurring in a 12-day-old and a 3-month-old infant respectively. Usually these defects do not become evident for years, and even decades, after birth That they then show a predilection for the metabolically more demanding proximal aorta suggests that they arise from impairment of the mechanism responsible for maintaining the integrity of the medial tissues Experimentally, this condition has been caused in rapidly *growing weanling* rats by incorporating *sweet pea meal in their* diet (Bachhuber and Lalich, 1955) In contrast, Duff (1932) observed no relation between the age and growth rate of the animals and the (much prompter) injurious effect of *diphtheria toxin* The report of Beaven and Murphy, of an unusually high incidence of dissecting aneurysm in hypertensive patients treated with *methonium* compounds if confirmed, gives grounds for speculating about an analogous metabolic influence in man

Schnitker and Bayer (1944) suggested a relationship between *pregnancy* and dissecting aneurysm since in their collected series more than half of 49 women younger than forty were pregnant Somewhat contrary evidence was furnished by Kinney et al (1945), who found that there was no increased incidence of dissection in 39 reported cases of coarctation in pregnancy

Infectious or granulomatous aortitis may be associated with dissecting aneurysm *Hypothyroidism* was suggested as a significant factor in the cases of Kountz and Hempelmann (1940); however, the dearth of substantiating data would indicate their findings to have been merely coincidence.

In the presence of medial disease and intramural hemorrhage, *mechanical factors* are important in the localization of the intimal laceration. Unusual stress occurs at two sites in the proximal aorta, which, according to Shennan are points of high incidence for the tears: (1) At the point where the right pulmonary artery crosses the aorta posteriorly, the posterior wall of the latter is regularly and rhythmically compressed by the systolic thrust of both channels. (2) The other site is the transition point from the relatively mobile arch to the fixed thoracic aorta where each pulsation results in localized bending stress.

MYCOTIC ANEURYSMS

Mycotic aneurysms are *localized dilatations of arteries* which result from infection and weakening of the vessel wall. The infecting source is usually intravascular, sometimes its origin is an extravascular focus in contact with the vessel wall Koch (1851) and Tufnell (1853) had reported earlier cases, but it was Osler (1885), describing multiple aortic aneurysms in a case of "malignant mycotic" endocarditis, who designated the lesions as *mycotic*. Since then, the term has come to be reserved for fungal infections, but tradition and long usage have perpetuated its application to a process which, with rare exceptions, is bacterial Although Osler was well aware of the bacterial nature of the endocarditis and the aneurysms in his case, Eppinger (1887) clearly established this bacterial origin and demonstrated that it was associated with inflammatory destruction of the vessel wall. This may occur by direct extension from an infected aortic valve or coarctation (so-called erosive aneurysm) or more remotely by an embolic mechanism The importance of embolization had been recognized by Virchow (1847) and Tufnell (1853) However, proper appreciation of its action awaited the dawn of the bacteriologic era. Minute infectious emboli may become entrapped in vasa vasorum and give rise to destructive inflammation of the vessel wall or, as Unger (1911) suggested, the infection may spread centrifugally from a nidus on the intimal surface.

TABLE 15-3 ASSOCIATED DISEASE IN 330 PATIENTS WITH A MYCOTIC ANEURYSM

Disease	*No of patients*
Bacterial endocarditis	291
Pneumonia	13
Osteomyelitis	6
Lung abscess	4
Septicemia (cause not stated)	4
Otitis media	4
Urinary sepsis	3
Meningitis	2

SOURCE: Goadby, McSwiney, and Rob, 1949.

The great majority of mycotic aneurysms are associated with bacterial endocarditis Almost 15 per cent of the latter complicate aortic coarctation. Other associated diseases are listed in Table 15-3.

The bacterial organisms which give rise to the associated aneurysms are the same as those causing the primary disease Alpha and hemolytic streptococci predominate, as they do in bacterial endocarditis, other common organisms are *Staphylococcus aureus, Diplococcus pneumoniae, Hemophilus influenzae,* and *Neisseria gonorrhoeae* Organisms tend to disappear from the lesions as they age The age and sex distribution of mycotic aneurysms reflect the incidence of the causative diseases, most cases occur in the second, third, and fourth decades Of 178 cases collected by Stengel and Wolferth (1923), 121 were in men and 57 in women

"Arteries in all parts of the body and of various sizes from the very largest to tiny unnamed vessels (the latter particularly in the brain), may be the seat of mycotic aneurysms Eppinger has called attention to their multiplicity stating that it is one of the most constant features of the condition" (Stengel and Wolferth) The aorta is most frequently involved, especially the root and the ascending segment. The pulmonary artery is relatively spared because of the infrequency of right-sided endocarditis. Table 15-4 lists the sites of 372 mycotic aneurysms

The type of endocarditis characterized by luxuriant *friable* vegetations is the form most likely to be complicated by embolic mycotic aneurysms Often there is widespread embolization and infarction. The size of the embolus determines the caliber of the vessel in which it lodges. Almost invariably embolic occlusion *involves vessels smaller than the aorta and* pulmonary arteries Favored sites of occlusion are *bifurcations, acute angulations,* or *points of rapid narrowing.* The mechanical effects of emboli are minor in the genesis of aneurysms, contrary to the opinion expressed before the role of bacteria was appreciated. The spread of infection from the embolus to the wall of the vessel results in inflammatory destruction, weakening, and subsequent focal dilatation (Fig 15-10). At times, this may happen so violently and so rapidly that there is rupture rather than herniation.

In large channels, occlusive embolization is less likely to occur and, except for direct extension (erosive aneurysm), infection of the vessel wall must take place in another manner. Direct penetration of the intact intima may be dismissed as unlikely; in the absence of an impacted shielding embolus, contact with circulating organisms could be, at most, fleeting These infections, therefore, arise from lodgment of septic emboli or bacteria in the vasa vasorum. *It will be recalled* that the nutrient arteries of the proximal aorta are derived from the coronary arteries, and this is the basis for

TABLE 15-4 LOCATION OF 372 MYCOTIC ANEURYSMS

Artery	*No of patients*
Aorta	119
Superior mesenteric	38
Cerebral	38
Femoral	22
Hepatic	20
Pulmonary	18
Splenic	15
Coronary	14
Heart valves	14
Posterior tibial	11
Common iliac	9
Popliteal	9
Radial	8
Ulnar	6
Renal	5
Axillary	5
Carotid	4
Basilar	4
Gluteal	3
Innominate	3
External iliac	2
Femoral profunda	2
Internal iliac, subclavian, and vertebral	1 each
Multiple lesions	55

SOURCE: Goadby, McSwiney, and Rob.

the particular vulnerability of the ascending aortic segment Coronary flow is maximal during diastole, and the proximity of their ostiums to the aortic valve makes them especially susceptible to embolization by fragments of vegetation broken off by the force of diastolic valvular closure The increased vascularization of the aorta which accompanies disease adequately explains its increased vulnerability to mycotic aneurysms

Mycotic aneurysms vary greatly in size and appearance They are usually small: millet-seed size in the cerebral arteries, no larger than a walnut in large arteries Occurring as they do in relatively young individuals, they are sharply demarcated from the contiguous, relatively undiseased arterial wall They are prone to rupture, this leads to free bleeding from aneurysms of cerebral, thoracic, or abdominal vessels and to perivascular hematomas or false aneurysms in peripheral lesions Arteriovenous fistulas are infrequent complications, bone erosion is not a feature of mycotic aneurysm

By the time the lesion can be examined, the infective embolus which led to it has often disintegrated, but when the embolus is demonstrable, its structure identifies it as a fragment or fragments of vegetation The inflammatory process in the vessel wall resembles that in the primary lesion, suppuration is uncommon There is an acute and subacute *periarteritis* and destructive *mesarteritis* Reparative reaction is poor and underlies focal dilatation and herniation of the vessel wall Within the sac, the intima is replaced by a fibrin membrane which may bear vegetations (Fig 15-10B). Microorganisms are demonstrable in acute lesions but become progressively more sparse thereafter While the entire process may be sharply delimited, there is often undermining of the adjacent intima Healing is usually associated with thrombosis and obliteration of the sac and, in peripheral arteries, the lumen as well Occasionally, as Eppinger described, there may be healing with reconstitution of the intima More commonly, healing is incomplete, and reflecting the smoldering nature of the infection, reparative changes of varying phases may be seen in individual as well as multiple aneurysms

Invariably, mycotic aneurysms develop in patients already ill, but the specific clinical findings associated with them depend upon the site of vascular involvement. If this lies deep within the body, the condition may not be suspected until post-mortem examination. However, a parasternal area of abnormal pulsation in a case of bacterial endocarditis permitted Stengel and Wolferth to make an antemortem diagnosis of mycotic aneurysm of the aortic arch The roentgenographic appearance enabled Nicholson (1940) to recognize a my-

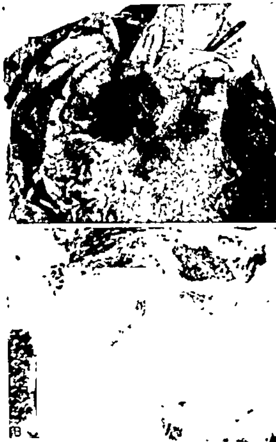


Fig. 15-10 A. Heart Mycotic aneurysm of right coronary artery. The probe passes from the ostium in the aorta through a transected part of the coronary aneurysm. Observe also the severe fibrinous pericarditis The patient, a victim of subacute bacterial endocarditis, died of pericardial hemorrhage. (*Courtesy Dr. Albert Hirst, Jr.*) B. Mycotic aneurysm of coronary artery. The vessel wall is entirely necrotic and can only be identified by the darkly staining elastic fibers to the right of the photograph. Proceeding to the left there is an abrupt bulge in the completely necrotic vessel wall (downward in the photograph). The aneurysm lining consists of fibrin admixed with purulent exudate; similar material permeates the periarterial tissues ×40

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External iliac	2
Femoral profunda	2
Internal iliac, subclavian, and vertebral	1 each
Multiple lesions	55

SOURCE. Goadby, McSwiney, and Rob.

cally, these cases are characterized by *primary degeneration of the lamina elastica of the media* more commonly than those of older people; the latter are characterized by *primary degeneration of the smooth muscle*, although both forms of degeneration commonly coexist (Gore, 1953).

Recently, the treatment of hypertension with potent ganglionic blocking drugs, particularly in the "malignant" phase, has been suggested as a cause for dissecting aneurysm of the aorta. In a single series of 44 patients so treated who ultimately succumbed and were examined at necropsy, 20 per cent had sustained this complication (Beaven et al.). Since this incidence greatly exceeds that expected in untreated cases, it was suggested that the fluctuations in blood pressure induced by the therapy, or a specific biochemical effect of the drugs, might be the means of its production. It seemed unlikely that prolonged life permitted by the therapy allowed the complication to develop when it would not have occurred otherwise In the author's experience, this high incidence of dissecting aneurysm during treatment of hypertension has not been observed

In other circumstances with fluctuating blood pressure, such as pheochromocytoma, dissecting aneurysm has occurred occasionally

CONGENITAL ABNORMALITIES. These commonly coexist with dissecting aneurysm, particularly when dissection occurs early in life, and may indicate a fundamental underlying weakness in the vascular system. The most commonly associated anomalies of the cardiovascular system are *coarctation of the aorta* and *bicuspid aortic valve*. Patients with *Marfan's syndrome*, which shows many disturbances of the body including arachnodactyly and dislocation of the lens of the eye, commonly succumb to dissecting aneurysm of the aorta The experimental production of dissecting aneurysm of the aorta by the feeding of legumes (*Lathyrus odoratus*) or their destructive principles (aminonitriles) also produces marked skeletal and connective tissue defects and suggests a general ground-substance disorder This observation led Bean and Ponseti (1955) to review their series of 20 cases of dissecting aneurysm studied at autopsy, they found concurrent skeletal deformities in 35 per cent This is a lead not well explored in

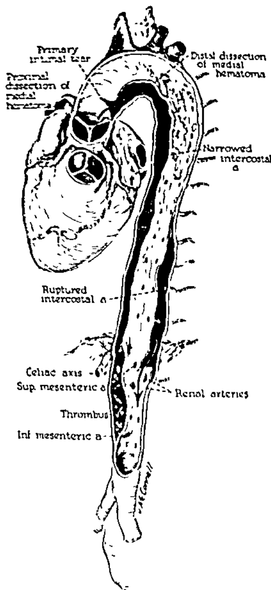


Fig. 15-11. Representation of dissecting aneurysm illustrating mechanisms which produce its clinical features

previous clinical reports, which may alert physicians to the diagnosis and stimulate investigators to further search for the causes of dissecting aneurysm.

STRESS Physical and emotional stresses, including hard manual labor, straining at stool, swimming, coitus, vomiting, and arguments, have immediately preceded the onset of the symptoms of dissecting aneurysm and may have facilitated the tearing of the aortic intima, allowing the blood to gush into and extend the preformed rent in its wall

cotic aneurysm associated with aortic coarctation. Lesions of the cerebral arteries lead to clinical findings indistinguishable from those due to other forms of cerebrovascular accident. In superficial or accessible vessels, the situation should be readily recognized. Lesions appear as pulsating inflammatory swellings a few days to several weeks subsequent to a sudden embolic onset. Some may rupture rapidly but, more often, several weeks elapse before hemorrhage is indicated by rapid enlargement, loss of distinct outline and painful tense swelling. Distally, arterial pulsation is often lost; but gangrene is infrequent.

The prognosis is that of the underlying disease and has improved enormously with the availability of antibiotics, yet rupture of a mycotic aneurysm was the principal cause of death in 17 of 408 penicillin-treated cases of subacute bacterial endocarditis. Prior to penicillin, Goadby et al. found only two reported recoveries from mycotic aneurysm and bacterial endocarditis. Aneurysms due to causes other than endocarditis were more often successfully treated Present-day treatment includes antibiotic administration for the infection and surgical excision of accessible lesions Prompt and effective treatment of bacterial endocarditis has undoubtedly reduced the frequency of bacterial aneurysms but these lesions may still appear, even after the completion of presumably adequate antibiotic therapy.

CLINICAL ASPECTS

DISSECTING ANEURYSMS

Definition. A dissecting aneurysm is a false sac within the wall of an artery, usually *the aorta*, less commonly *the pulmonary artery, a branch of the aorta*, or, rarely, *a smaller artery*. Ordinarily the false sac is penetrated by the circulating blood column from the lumen of the vessel, the pressure of which frequently distends the sac until it ruptures, either outwardly (through the adventitia) or inwardly (reentering the lumen through the intima) Burchell calls the lesion *"a dissecting hematoma"* because of the absence of a true expanding and limiting wall characteristic of other aneurysms. Nevertheless, two centuries of designation as a dissecting aneurysm will probably preserve this term with the understanding that it refers to *a false aneurysm* (Fig. 15-11).

History. The earliest recognition of dissecting aneurysm was by the morbid anatomists of the seventeenth and eighteenth centuries (Sennert, Morgagni) but its clinical recognition has come only within the last century (Latham). The ruptured aneurysm, an obvious cause for sudden death, was a gratifying and encouraging finding for the early anatomists and served to justify and promote dissection-study of human remains At least two of Morgagni's cases of aortic aneurysm rupturing into the pericardial sac appear to have been of the dissecting type. Nicholls' report of the post-mortem examination of King George II of England (1760) shows that the king had a dissecting aneurysm of the aorta, although his death resulted from rupture of the right ventricle. Latham et al. (1856) reported their ante-mortem diagnosis of a dissecting aneurysm of the aorta affecting a 51-year-old man, who was seized with "a sudden and violent pain as though . . . his chest were torn open . . . seemed to dart . . . down the left side of the spinal column . . . after a repetition of the lacerating pain . . this time . . from scapula to scapula . . ," and confirmed this clinical diagnosis by observation of the aorta after the patient's death. In the century which has passed since this first diagnosis of a dissecting aneurysm of the aorta was made, the frequency and accuracy of its recognition has improved but it is still identified in only one-fourth to one-half of the cases which occur

Cause. Dissecting aneurysm occurs mainly during later life; the average age at onset is about 50 years It has been described at both extremes of life, in a patient of 100 years (Shennan) and in an infant of 12 days (Wolff). It affects men at least twice as frequently as women, except in the eighth and ninth decades when it is women who are predominantly affected (Shennan) It is more common in the white race.

HYPERTENSION. Ordinarily, elevated blood pressure precedes the development of dissecting aneurysm of the aorta and commonly persists after the dissection occurs unless masked by shock. In most instances, the heart has already hypertrophied before dissection takes place. In persons under 40 years of age, hypertension is not so uniformly present. Pathologi-

within the first few days Nontraumatic ecchymoses are occasional but striking findings resulting from local disturbances in circulation.

Systemic hypertension almost uniformly precedes the acute episode, except in the occasional cases which occur early in life It commonly persists as an important physical finding after the acute episode and should be expected, unless masked by the severity of the clinical shock. *It is remarkable how high the blood pressure may be, even when the patient appears to be suffering from shock*, a paradox useful in diagnosis. In those instances where the shock syndrome has concealed the hypertension from the examiner, its previous presence is evidenced by retinal arteriolar changes Except in young persons, *left ventricular enlargement* is almost always present The left ventricle is more accessible to examination than under normal circumstances, in that its activity is transmitted to the chest wall with unusual clarity and fidelity The apex is displaced downward and toward the left. The pressure of the enlarged left ventricle upon the diaphragm changes its mechanical advantage upon the lower rib cage, impairing excursion of the medial portion of the left costal margin When associated dilatation is advanced, systolic retraction medial to the apex results from increased ejection and produces *a see-saw motion of the chest wall* with its fulcrum about an inch medial to the maximal apical thrust.

The sudden development of *an aortic diastolic murmur*, often with concurrent *systolic murmur*, in the presence of the other clinical features, is virtually pathognomonic for dissecting aortic aneurysm. It may result from aortic valvular distortions produced by the dissecting hematoma (the usual explanation cited for this sign) but may also occur when the hematoma does not distort the valves (Resnik et al) Letulle explains that the ingress and egress of blood from the false sac, with the rising and falling pressure of the true lumen of the aorta, can cause the double murmur in the instances where no valvular distortion is demonstrable This may be the actual cause for this sign in all cases. Unfortunately, this valuable sign is not uniformly present, if found, it will confirm the diagnosis

The widening of the aorta is not easily demonstrable by physical examination, but its pulsations, better transmitted by the wide, false sac to the chest wall, may become conspicuous. Logue et al (1952) demonstrated that a transmitted pulsation of the sternoclavicular joints was diagnostic of dissecting aneurysm when the clinical findings were otherwise consistent and when syphilitic aneurysm, partial rupture of saccular aneurysm of the aortic arch, and anomalous right aortic arch could be excluded by other means. Secondary rupture of the false sac into the pericardium rapidly produces *cardiac tamponade* and frequently immediate death. Prompt increase in venous pressure and congestion, paradoxical pulse, faint heart sounds, some increase in heart dullness with reduction in the accessibility of the ventricular pulsations, a friction-rub, and falling blood pressure, are the evidences of tamponade. Rupture into the pleural space, more commonly the left, gives the signs of free pleural fluid

Sometimes abdominal symptoms and findings predominate to such an extent that a primarily "surgical" catastrophe within the abdomen seems to be present. Since the vascular supply to any abdominal organ may be occluded by the dissection, almost any acute abdominal emergency can be simulated. The syndrome depends upon the course of the dissection, the organ rendered ischemic, and the site and extent of extravascular hemorrhage. Peritoneal irritation arises from seepage of blood into the abdominal cavity, this, together with the concurrent pain and vomiting, may encourage the surgeon to explore the patient fruitlessly and with great mortality risk

Paralysis of the extremities, particularly the legs, arises from both occlusion of their major vessels by the dissection and spinal-cord damage incident to interruption of the intercostal, lumbar, and anterior vertebral arteries. When the major vessels to the extremity are occluded, there is motor and sensory paralysis, absent pulse, pallor, and clamminess of the skin, which is sometimes marbled or shows a mottled cyanosis Distal gangrene may supervene. *Spinal-cord damage* results in neurological changes below its level, it is manifested by weakness, paresthesias, pain, sensory and reflex changes, and sometimes inability to void.

Neurological alterations referable to the brain often coexist with dissecting aneurysm and result from both interruption of vertebral and

MISCELLANEOUS *Pregnancy* appears to be a contributing factor (Mandel et al.), since half of the women affected by dissecting aneurysm before the age of 40 years were either pregnant or in the early puerperium at the time the dissection occurred.

A few cases of dissecting aneurysm have been reported following *total thyroidectomy* in patients with severe hypertension (Kountz et al). It has been suggested that further observation may demonstrate a relationship between the endocrine glands and aortic cystic degeneration.

Arteriosclerosis often coexists with dissecting aneurysm of the aorta, as might be expected from the age at which most dissections become manifest. Syphilis, though previously under suspicion, is no longer considered to be a prominent factor in the causation of dissecting aneurysm

Symptoms. Pain is the outstanding symptom of aortic dissection, occurring in almost every patient who remains conscious and out of profound shock. The pain ordinarily begins in the anterior chest, arising beneath the sternum and extending into the back, particularly into the interscapular areas Its onset is usually sudden, often coinciding with exertion, vomiting, emotional display, or other stresses Ordinarily severe and terrifying, the pain is usually of a *tearing* quality, which suggests to the patient that he has suffered internal damage placing his life in immediate peril *The pain spreads*, as would be anticipated from the course of the dissection, *into the head and neck, abdomen, or the extremities* Occasionally, it is felt predominantly or exclusively in the back or abdomen, less commonly it is limited to the head, neck, or extremities The pain is persistent and little affected by external circumstances or the physiological functions of other parts of the body. It even resists fairly large doses of narcotic drugs

A *shock syndrome* with profound prostration may overshadow the patient's pain, and in some instances is the presenting complaint It is an outstanding clinical accompaniment in one-third to one-half of the cases The blood pressure recorded is often higher than symptoms would lead one to anticipate because of the significant elevation which antedated the dissection; a considerable fall still allows a fair level of blood pressure to remain.

Dyspnea is an important clinical expression of the disease in approximately one-half the patients. It attracts special attention because the usual respiratory symptoms and findings which accompany dyspnea resulting from other causes are absent. *Cyanosis* appears occasionally.

Neurological symptoms are fairly frequent and often helpful diagnostically. *Confusion* and *disorientation* affect up to one-third of the patients. *Coma* and *collapse* affect up to one in five patients after aortic dissection Neurological reactions arise from both the altered perfusion of the brain and spinal cord incident to the shock syndrome and the obstruction of the lumens of major vessels from the pressure of the expanding hematoma. *Paresthesias*, especially of extremities, are the complaint of one patient in ten and contribute diagnostic clues localizing the lesion. *Weakness* of the lower extremities, with or without sensory changes, may occur; this arises from occlusion of the lower aorta and its branches with resultant ischemia of the extremity itself, or from occlusion of intercostal vessels with resultant spinal cord ischemia or infarction *Hoarseness* from recurrent laryngeal nerve involvement occurs only occasionally but helps make the diagnosis when present.

Signs. Immediately following an acute dissection of the aortic media, the patient's appearance indicates an acute catastrophe He is anxious, fearful, and pale (with an *ashlike grayness*), perspires on a cold, clammy skin and breathes rapidly, often grunting during respiration. There is a rapid pulse which may be either thready or full. There may be a *reduplication of pulse* in a carotid artery (Nissim, 1946) or other arteries, the second pulsation representing a transmission delayed by expansion of the hematoma. A difference in the blood pressure in the arms, or reduction of the relative blood pressure in the legs, may result from partial occlusion of the aortic lumen by the medial hematoma

In occasional cases, particularly where the dissection has been of lesser degree or the onset more gradual, the shock syndrome is less evident The course of the shock, once present, is quite variable, sometimes spontaneously abating after a few hours but often severe and progressive until death.

Initially fever is absent but usually develops

vals, sagging of the S-T segment, and flattening and inversion of the T waves. A completely normal electrocardiogram is unusual in dissecting aneurysm and should lead one to question the clinical diagnosis.

Radiographic findings in dissecting aneurysm of the aorta, although rarely diagnostic in themselves, are often helpful. Unfortunately, the precarious clinical condition of the patient often precludes taking the patient to the radiology department. Bedside techniques, particularly if the patient must be kept recumbent or the tube must be brought closer than 6 ft, frequently induce such distortion for the finished roentgenograms as to make them valueless. Widening of the aortic shadow is the most common radiographic expression of dissecting aneurysm, aside from the usual concurrent left ventricular enlargement. If, luckily, previous chest films are available, their technique should be repeated as to patient position, exposure factors, and respiratory phase, so that comparison of the aortic shadows can confirm the diagnosis If intimal calcification is fortuitously present, the thickness of the aortic wall (normally 2 to 3 mm) can be measured readily and any increase due to the medial hematoma can be appreciated In some instances, the true lumen of the aorta has been outlined by angiocardiographic techniques which accurately delineate the site and extent of dissection, but the hazards of these techniques require sober consideration In chronic dissecting aneurysm, calcification of the limits of the false sac rarely occurs but, if present, outlines the sac clearly for diagnostic consideration. The blood column of the true aortic lumen produces a denser radiographic shadow than the dissected portion and thereby facilitates its identification. The false sac may pulsate but does not do so invariably. Serial examinations which allow identification of advancing dissection, particularly around major aortic branches, may confirm the diagnosis but are extremely difficult to obtain in the usual patient because of the gravity of his illness

Course and Prognosis. The usual course of dissecting aneurysm of the aorta is short, death commonly occurs within an hour to a fortnight after the onset, with the patient in a state of circulatory collapse. Death may be accelerated by congestive heart failure, uremia, pulmonary infection or infarction, and neurological complications Death may be delayed and in occasional instances avoided when secondary rupture of the false sac into the vessel fortuitously allows reentry of the blood through the intima into the lumen of the vessel. Such a reentry, while prognostically favorable, does not invariably prevent the external rupture and resultant exsanguination or the secondary proximal rupture into the pericardium with cardiac tamponade. Occasional patients have lived several months and even (rare instances) several years after the initial dissection; in these instances death has resulted ultimately from other causes, but most commonly from further dissection or congestive heart failure.

Differential Diagnosis. Dissecting aneurysm, because of its polymorphous distribution, course, gravity, and relative infrequency, simulates many other disorders and often leads the physician into a diagnostic trap. It is most commonly confused with myocardial infarction or pulmonary embolism. It often simulates various abdominal catastrophes and motivates useless, hazardous surgical intervention. Neurological and peripheral vascular syndromes need to be carefully distinguished Guided by familiarity with the manifestations of dissecting aneurysm, aware of its ability to mimic more frequent disorders, and prepared by its inclusion for differential consideration in the several syndromes which it may present, the physician will recognize this disease more frequently and mistreat it less often. The progression of symptoms and findings, consistent with the results of an expanding medial hematoma with progressive occlusion of sequential branches of the aorta, is very helpful to the physician attempting to diagnose the patient's illness.

Treatment. Conservative treatment for dissecting aneurysm is primarily supportive and symptomatic. It includes bed rest, morphine, and oxygen. All available means for combating the profound shock are often found wanting Blood transfusions will partially replace the loss into the false sac and through external rupture. Pressor amines which avoid concurrent increase in myocardial irritability, such as levarterenol (Levophed), metaraminol (Aramine) and mephentermine (Wyamine) have been extensively employed Since all that pressor amines can accomplish is reduction in the volume of the vascular bed, it is not remark-



Fig. 15-12. Electrocardiogram made a day after symptoms of dissecting aneurysm of the aorta appeared. The tiny Q_2 and deeper Q_3-aVF, and the elevated S-T segments suggest a diagnosis of posterior myocardial infarction Nonspecific T-wave inversion in anterior and lateral leads suggest ischemic changes difficult to reconcile with a posterior infarction alone. Two days after this electrocardiogram was taken, death occurred from proximal extension of a dissecting aneurysm of the aorta and rupture into the pericardium The left coronary artery was caught in an ecchymotic and suffused area at the base of the aorta so that its lumen was compromised by the extrinsic pressure; this explains the simulation of ordinary myocardial infarction.

carotid circulation by the pressure of the aneurysmal mass and concurrent vascular disease of the brain independent of the dissecting aneurysm. Hemiplegia, hemiparesis, convulsions, disturbed consciousness, vertigo, aphasia, and blindness may occur The neurological findings are often bizarre and difficult to correlate, even when the detailed anatomical findings are available. Their unusual character should suggest the diagnosis.

The frequency of neurological changes recorded varies widely in different series of patients and somewhat with the enthusiasm with which they are sought. About one-half the cases will yield abnormal data after careful examination. While, in many instances, the neurological alterations are nonspecific by themselves, they greatly support the diagnosis when the clinical picture is otherwise compatible.

Laboratory Findings. Leucocytosis is usually found within a few hours after aortic dissection and frequently approximates 20,000 cells/mm^3. Marked leucocytosis ranging around 30,000 cells sometimes occurs; occasionally higher levels are noted *Normochromic anemia* is common. The urine is frequently abnormal, with albumin, casts, and red blood cells demonstrable in most cases. With frank involvement of the renal arteries, *gross hematuria* is usually present as well as a concurrent rise in the nitrogenous residues of the blood *Jaundice* is occasionally present. When *pleural effusion* is present, thoracentesis frequently produces bloody fluid. In some instances, a blood-tinged pleural fluid occurs without frank perforation of the false sac of the aneurysm.

The serological tests for syphilis are ordinarily negative and, even when they are positive, no relationship of syphilis to dissecting aneurysm seems likely. Actually, the inflammatory lesions of luetic origin probably render dissection less likely because scarring tends to fuse the layers of the aorta together.

Electrocardiograms are usually abnormal but without specificity for this lesion. Various disturbances of rhythm, including atrial fibrillation, and disturbances of intracardiac conduction may be present The most common electrocardiographic alterations are those of the concurrent left ventricular hypertrophy (Levinson et al) An erroneous electrocardiographic diagnosis of myocardial infarction is frequently made from nonspecific S-T and T-wave changes In about one-fourth of the cases, there are patterns indicating coronary insufficiency Compression of a coronary artery by hematoma, most commonly a vessel of the posterior wall (as occurred in the instance of which the electrocardiogram is shown, Fig 15-12), compromises the lumen and produces pathological alterations in the myocardium identical with those caused by occlusion of the coronary lumen. Blood leaking into the pericardium produces the typical pattern of pericarditis In instances where kidney damage has resulted, electrocardiographic alterations are those seen in uremia and electrolyte disturbance, including prolonged Q-T inter-

reports (Table 15-6), more than one-half involved the aorta, intracranial, superior mesenteric, or femoral arteries. Any artery in the body may be attacked Mycotic aneurysms may be multiple (394 aneurysms in 350 cases) and would probably be multiple more frequently were it not for their own lethal course, as well as for the underlying mortal disease They are usually saccular, varying greatly in size They frequently rupture and bleed massively or may serve as the site for a thrombus which occludes the lumen of the vessel of origin. Histologically there is destruction of the vessel wall which is invaded by acute and chronic inflammatory cells

Clinical Features. In the usual case, a mycotic aneurysm arises in a patient who already shows signs of a serious, septic systemic disease The length of illness preceding its onset is variable, depending upon the virulence of the primary infection. The patient has usually lost weight and displays general malaise, lack of energy, fever, and a sallow complexion Endocarditis, usually with bacterial involvement, is commonly present. The course of the underlying disease is suddenly interrupted by an embolic episode characterized by local pain, signs of ischemia peripheral to the occlusion, increase in pulse rate, and fever. Later, as the embolic signs begin to subside, there is a recrudescence of local signs including increase in pain and development of a pulsating mass often manifesting a *bruit* Rupture may occur after a variable period of time, often within a week after its origin, or the aneurysm may thrombose and go on to spontaneous healing by fibrosis In some instances, the several stages may follow in such rapid succession that massive bleeding appears to herald its onset

The clinical syndromes presented by mycotic aneurysms in specific locations are distinctive When the *abdominal aorta* is involved, there is usually deep visceral pain, sometimes associated with a pulsatile mass and thrill. There may appear to be an acute intraabdominal "surgical" catastrophe, particularly when rupture produces shock or bleeding into the bowel Mycotic aneurysm of other intraabdominal arteries, such as the mesenteric, hepatic, or splenic, present similar pictures When the *thoracic aorta* is involved, there is deep substernal chest pain, often compression of contiguous structures, and often rupture with sudden death Rupture may occur into the trachea or esophagus with resultant bloodspilling, either into a pleural cavity (usually the left) with the rapid development of bloody fluid compressing the lung, or into the pulmonary vessels with resultant pulmonary hypertension and hemoptysis It may simulate other acute thoracic catastrophes, such as myocardial infarction, pulmonary embolism, or dissecting aneurysm of the aorta When *intracranial arteries* are involved, the syndrome often simulates the rupture of a congenital aneurysm with subarachnoid bleeding, or it may resemble an ordinary intracranial hemorrhage with hemiparesis or hemiplegia *Headache* may precede other symptoms. It is particularly true of intracranial involvement that the course is often exceedingly short and with the several stages of aneurysm formation telescoped one upon the other, so that the massive bleeding first announces the disease When a vessel of an extremity is involved, particularly

TABLE 15-6 LOCATION OF ANEURYSM IN A SERIES OF 350 CASES (394 ANEURYSMS)

Location	*No of cases*	*Cases, %*
Aorta	132	33
Intracranial	46	12
Superior mesenteric	38	10
Femoral	23	6
Hepatic	20	5
Pulmonary	18	5
Splenic	16	4
Coronary	11	4
Endocardium, valvular	14	4
Tibialis, posterior	11	3
Iliac, common	9	
Popliteal	9	
Radial	8	
Ulnar	6	
Carotid	6	
Renal	5	
Axillary	5	
Gluteal	3	
Innominate	3	
Iliac, external	2	
Femoral, profunda	2	
Iliac, internal	1	
Subclavian	1	
Vertebral	1	
Arterial branch in wall of gall bladder	1	

SOURCE Compiled from published reports

able that their action is only temporary and is soon overcome by the further progress of the disease.

Anticoagulant therapy is ordinarily considered to be contraindicated because it destroys the clotting potential of the individual and his ability thereby to seal small ruptures in the arterial walls. For this reason, differentiation of dissecting aneurysm from myocardial infarction, where such therapy is commonly employed, has been considered of greatest importance. Recently Freeman (1956) has suggested a reevaluation of this concept, suggesting that anticoagulant therapy might be a useful adjunct facilitating reentry of the blood from the false sac by a secondary intimal defect, either spontaneously or surgically, back into the true lumen. It is dubious whether the clotting potential of the individual is much protection when external rupture of a dissecting aneurysm occurs and it is not likely that clotting within the false sac is much protection either. Nevertheless, until further experience has been accumulated, it is generally recommended that anticoagulants be withheld from such patients.

The inadequacy of conservative measures in the control of the shock and the frightfully poor prognosis has encouraged surgeons to try a number of heroic mechanical procedures for correcting the defect. In general, these procedures include the creation of a secondary ostium communicating with the true lumen of the vessel near the lower end of the false sac, with closure of any remaining sac beneath this ostium with or without resection of a portion of the involved aorta and replacement by homograft or other aortic substitute. In a few instances, the results of such operations have been gratifying (DeBakey et al.; Swan et al., 1950) for the short period of subsequent observation. Their eventual worth will be better evaluated after more cases have been followed for a longer time. Unfortunately, the risk of such procedures is great as might be anticipated from the poor clinical condition of the candidates, the magnitude of the procedure, and the natural history of the disease.

TABLE 15-5 SOURCE OF INFECTION IN 350 CASES OF MYCOTIC ANEURYSM

Disease source	*No of cases*	*Cases, %*
Endocarditis, bacterial (acute and subacute)	305	87
Pneumonia	15	4
Osteomyelitis	6	2
Septicemia (of various other origins)	6	2
Lung abscess	4	1
Otitis media	4	1
Infection of the urinary tract	3	1
Meningitis	2	
Sinusitis, sphenoidal, acute	1	
Cryptococcosis	1	
Lymphadenitis, tuberculosis	1	
Primary (in congenital hypoplasia of aorta)	1	
Arthritis, gonorrheal	1	

SOURCE: Compiled from published reports.

MYCOTIC ANEURYSMS

A mycotic aneurysm is an abnormal local dilatation of an artery weakened by a suppurative process, produced by infection, within its wall. The term "mycotic" was applied by Osler (1885) to distinguish those aneurysms which result from infection from the larger group of aneurysms which result from degeneration or trauma The term *mycos* (derived from the Greek μυκος meaning mushroom or fungus) may be considered inappropriate because most of these aneurysms arise from bacterial infections, principally from streptococcal emboli of bacterial endocarditis, pneumonia, septicemia, or abscesses, rather than from fungus infection, such as actinomycosis or cryptococcosis, from which they rarely originate, but its authoritative origin and long usage will probably preserve its designation as "mycotic."

Origin. Most mycotic aneurysms afflict young men Three out of four patients affected are men, and nine out of ten are under 40 The source of the infection may be any suppurative focus within the body but in more than 90 per cent of cases is bacterial endocarditis or pneumonia (Table 15-5). Preexisting vascular defects, such as coarctation or damage to the vessel wall, facilitate aneurysm formation but are not prerequisite.

Pathology and Pathogenesis. The majority of mycotic aneurysms result from the infection carried to the wall of a major artery by a bacterial embolus. The few others arise from the direct extension of a neighboring abscess In the series of 350 cases compiled from published

7

Aortic aneurysms

K. K. DATEY

The word "aneurysm" is derived from the Greek word "aneurusma," which means "to widen" or "to dilate"

Aneurysms, chiefly *traumatic*, were known to Galen Fernel (1554) was the first to associate arterial dilatations with aneurysms. Both Fernel and Paré (1564) associated aneurysms with syphilis. Morgagni (1761) further emphasized the role of syphilis in the development of aneurysms of the aorta Riva (1670) discussed the nature and character of aneurysms while Lancisi (1707) discussed their causes and types *Fusiform aneurysms* of the aorta were demonstrated by von Haller in the eighteenth century Nicholls (1761) reported the post-mortem findings in a case of dissecting aneurysm of the thoracic aorta Hunter (1762) described *arteriovenous fistulas* The discovery of *Treponema pallidum* in sections of tissue from patients with syphilitic aortitis and the development of the Wassermann reaction, were further milestones Lately, an increasing awareness of the condition and the development of modern diagnostic techniques, e g., electrokymography, angiocardiography, aortography, and cardiac catheterization, have made the detection of aneurysms more definite, this is particularly true of aneurysms of the sinus of Valsalva, which hitherto were usually undiagnosed ante-mortem. Major progress in the field of aneurysms is represented by the development of modern surgical methods (replacement by grafts, etc), which have revolutionized their treatment.

DEFINITIONS

An aneurysm may be defined as a localized or diffuse abnormal outpouching of an artery. An aneurysm of the aorta may be "true" or "false." A "true aneurysm" is one in which the walls of the dilatation are formed by the coats of the artery. The term "false aneurysm" is applied to those dilatations in which the wall has undergone rupture, but exsanguinating hemorrhage has been prevented by the restraint of adherent adjacent structures, which have formed a new false wall. True aneurysms may be of the following types:

1. *Diffuse aneurysm* This implies generalized dilatation of an artery.

2 *Saccular aneurysm* Saccular aneurysms are saclike dilatations which communicate with an artery by an opening that is small in comparison with the size of the sac Such dilatations are restricted to a segment of an artery or part of its circumference

3 *Other aneurysms* The aorta may establish communication with a vein, the pulmonary artery, or the chambers of the heart (either a ventricle or an atrium). These communications have also at times been included under aortic aneurysms

False aneurysms are best exemplified by the *dissecting aneurysms*. These are caused by splitting of the media of the aorta by extravasated blood that has penetrated between its coats from the lumen of the vessels or from the vasa vasorum.

INCIDENCE

Aneurysms are found in about 1 to 3 per cent of all bodies submitted for autopsy.

Age. About 90 per cent of aortic aneurysms are detected in patients between 40 and 70 years of age In a series of 230 aortic aneurysms syphilitic involvement was the predomi-

the femoral artery, the serial stages of aneurysm formation, from the initial embolism through that of the expanding painful expansile mass to rupture or healing by fibrosis, are most easily seen. The onset is frequently characterized by pain, numbness, coldness, pallor or mottled cyanosis, imperceptible arterial pulses below the lesion, collapsed superficial veins, and loss of the motor power in the leg. Later, there is recrudescence of pain with an expanding tumor mass at the site of the initial embolism, often a bruit, peripheral edema, and signs of peripheral neuropathy from compression of the nerves The bleeding after rupture follows the fascial planes of the leg which often limit the extent of hemorrhage and form a false sac Death from *shock* is frequent. In rare instances, a mycotic aneurysm may rupture into the adjacent vein, thereby forming an *arteriovenous fistula* which can later cause cardiac failure In those instances where the aneurysm becomes thrombosed, fibrosis later occurs but leaves the extremity with chronic arterial insufficiency

The laboratory findings in patients with mycotic aneurysm show the usual alterations expected with infection. The specific causative organism can often be cultured from the blood, or, after surgical removal, from the wall of the aneurysm. Roentgenograms, though often unnecessary, may reveal the outline of the aneurysm, particularly in the thorax, and, after proximal injection of contrast material into the artery, will indicate the exact location of the lesion.

TREATMENT

Many mycotic aneurysms can be prevented by adequate treatment of the primary infection. Frequently, suitable *antibiotics* will curtail the growth of the organism, so that it will be unable to continue to destroy the arterial wall. After appropriate antibiotic therapy, therefore, the aneurysm may not develop despite the lodgment of a septic embolus, or will cease to expand once it has started. In some instances, however, the aneurysm already may be fully formed before suitable prophylactic therapy can be effective In such instances, surgical intervention is essential to remove the aneurysm. Sometimes, special procedures are necessary to reestablish the continuity of the vessels Preliminary or subsequent *sympathectomy* may be necessary to insure adequate circulation distal to the area involved by the aneurysm. Regardless of the therapy employed for the treatment of the aneurysm itself, the patient requires prolonged treatment and convalescence in order to overcome the underlying infection and recover from the ravages of a severe generalized illness.

Pressure on Nerves. Pain due to pressure on the nerve roots is neuralgic in type. Pain in the neck is probably caused by abnormal afferent impulses reaching the cervical spinal cord as a result of distention of the transverse arch. Aneurysms of the descending aorta are more likely to press on spinal nerve roots

Coronary Pain The involvement of coronary vessels, particularly at their openings in the sinus of Valsalva, may produce pain which in character and distribution is similar to and indistinguishable from "angina pectoris"

NEUROLOGICAL MANIFESTATIONS *Left Recurrent Laryngeal Nerve.* This nerve, because of its close proximity to the aortic arch, is frequently involved in aneurysms of the arch The abductor fibers are involved earlier than their adductor counterparts and therefore *the left vocal cord is, at first, in the position of adduction* During phonation, the right vocal cord meets the left and thus the voice may remain normal. Hence, a laryngoscopic examination is necessary to detect, at an early stage, the involvement of the left recurrent laryngeal nerve, since this may be associated with even a small aneurysm. Later, as the pressure increases, adductor fibers are also damaged, and consequently the left cord remains immobile in "cadaveric position," midway between full inspiration and full expiration. It is at this stage that the patient develops *hoarseness,* which is present in about 20 per cent of patients with aneurysms of the arch. Hoarseness may be the first presenting symptom The voice may

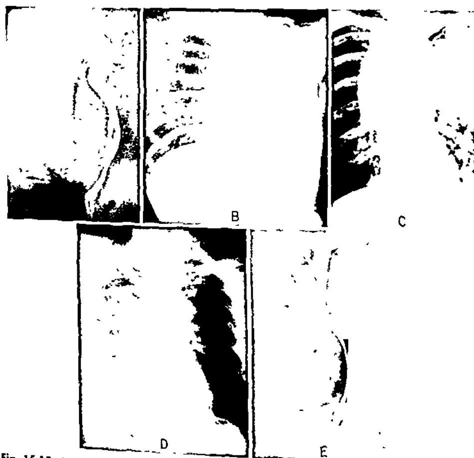


Fig 15-13 A Lateral view of the spine, showing erosion of a thoracic vertebra with intact intervertebral disk There is forward displacement of the esophagus B PA view of the chest, showing collapse of the left lung as a result of pressure caused by aortic aneurysm. C Aneurysm of ascending aorta, arch, and descending aorta, showing bronchiectatic changes in the lower lobe of the left lung D Aneurysm of the ascending aorta and arch of the aorta, showing fluid in the right pleural cavity. E. Lateral roentgenogram showing forward displacement and narrowing of the lumen of the esophagus caused by an aneurysm of the aorta

TABLE 15-7. PERCENTAGE DISTRIBUTION OF AORTIC ANEURYSMS

Location of aneurysm	*Author's series (Datey) (63 cases)*	*Turner's series (146 cases)*
Ascending aorta	32	70.5
Aortic arch	40	
Descending aorta	12	18.5
Abdominal aorta	7	5.5
Multiple aneurysm (Including aneurysms of the aortic bulb in author's series)	9	5.5

nant cause and accounted for 82 per cent of the cases, atherosclerosis for 14 per cent, combined syphilis and atherosclerosis for 1.3 per cent; and mycotic and traumatic for the rest. Most of the arteriosclerotic aneurysms were located in the abdomen (63 per cent), while the aortic arch and thoracic aorta were involved in 37 per cent of the cases. Of the syphilitic aneurysms, however, 89 per cent were in the thoracic aorta (85 per cent of these in the ascending aorta and arch, 15 per cent in the descending aorta), while the abdominal aorta was involved in only 11 per cent

Distribution. Table 15-7 indicates the distribution of aortic aneurysm as found by Turner and the author in series of 146 and 63 cases, respectively

ANEURYSM OF THE THORACIC AORTA

The aorta may undergo two types of dilatations, viz., the diffuse and the saccular (or circumscribed).

Diffuse Aneurysm. General dilatation of the aorta (diffuse aneurysm) is often extensive, but seldom reaches an enormous size Such an aneurysm may be associated with diminished coronary circulation, which in turn leads to cardiac pain Pulsations may be visible in the suprasternal notch. The roentgenogram shows unfolding and general dilatation of the aortic arch When the aortic ring is not stretched, the dilatation of the aorta beyond it may produce a systolic murmur. If there is no complicating aortic incompetence or associated coronary disease, patients with diffuse aneurysms may lead a normal span of life without much disability.

Saccular (Circumscribed) Aneurysms. These are almost always caused by syphilis and are present in about 30 per cent of all cases of cardiovascular syphilis. However, syphilis may also give rise to a fusiform dilatation of the aorta. Syphilitic aneurysms are usually single, varying from a few centimeters to more than twenty in diameter. Occasionally, small daughter aneurysms project from the main mass.

SIGNS AND SYMPTOMS

Aneurysms of the aorta are remarkable in that a large aneurysm may be present and persist for several years without producing clinical manifestations. The signs and symptoms depend upon the site and size of the aneurysm The general clinical features of aneurysms will be discussed first, then the characteristics of aneurysms at different locations. In general, the clinical features include the pressure syndrome, physical signs due to mass, altered circulatory dynamics, and the rupture syndrome.

Pressure Syndrome. PAIN. Pain is the most common and earliest symptom of aneurysm of the aorta and is present in more than 60 per cent of cases. In aneurysms of the arch, pain may be felt in the retrosternal region, left side of the neck, occipital region, or back, and may radiate down the left arm or both arms In aneurysms of the descending thoracic aorta, pain is located posteriorly in the lower part of the thorax and in the loins Pain is not a feature of aneurysm of the ascending aorta until the sac erodes the bone (either sternum or ribs) The pain is usually persistent, "neuralgic" in type, or it may be intermittent and dull *The pain is markedly influenced by any change of posture*, particularly in aneurysms of the arch and descending aorta.

Pressure on Bones This produces a continuous, agonizing, and boring pain. Such a pain is produced by pressure on the ribs or sternum by aneurysms of the ascending aorta and arch, and on the spine and ribs by aneurysms of the descending aorta Pressure on the vertebrae results in destruction of their bodies while the vertebral disks remain intact (Fig. 15-134). Erosion of the ribs may occur without pain (although this is rare), and occasionally pain disappears after the erosion of a rib is complete.

Pressure on Nerves Pain due to pressure on the nerve roots is neuralgic in type. Pain in the neck is probably caused by abnormal afferent impulses reaching the cervical spinal cord as a result of distention of the transverse arch. Aneurysms of the descending aorta are more likely to press on spinal nerve roots

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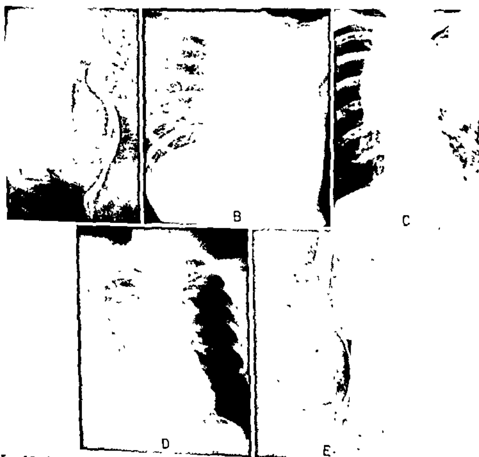


Fig. 15-13. A Lateral view of the spine, showing erosion of a thoracic vertebra with intact intervertebral disk There is forward displacement of the esophagus B PA view of the chest, showing collapse of the left lung as a result of pressure caused by aortic aneurysm. C. Aneurysm of ascending aorta, arch, and descending aorta, showing bronchiectatic changes in the lower lobe of the left lung D Aneurysm of the ascending aorta and arch of the aorta, showing fluid in the right pleural cavity E. Lateral roentgenogram showing forward displacement and narrowing of the lumen of the esophagus caused by an aneurysm of the aorta

be muffled, husky, cracked, *hoarse*, or tremulous; later, *aphonia* may supervene.

Right Recurrent Laryngeal Nerve. In rare instances the right vocal cord may be paralyzed if the aneurysm extends to the subclavian artery and presses on the right recurrent laryngeal nerve.

Phrenic Nerve. Irritation of the phrenic nerve may give rise to *hiccup* and later may (rarely) even produce *paralysis* of the left dome of the diaphragm, which is *raised*; paradoxical movements are observed on fluoroscopy.

Sympathetic Nerves. As with other nerves, pressure on sympathetic nerves first produces irritation and later paralysis During the stage of irritation, *the ipsilateral pupil is dilated* and there may be associated sweating and flushing on the same side of the face, ear, and at times the upper extremity During the stage of paralysis, *the pupil of the affected side is smaller than that of the opposite side,* there may be enophthalmos, and a slight degree of ptosis is present. These pupillary changes may also be due to differences in the blood pressure of the carotids (the pupil may be dilated on the side of the carotid with lower pressure). Syphilitic lesions of the central nervous system may also produce *inequality* of the pupils (*Argyll Robertson sign*).

Intercostal Nerves An aneurysm that presses backwards and erodes the vertebrae and posterior portions of the ribs is likely to press upon the intercostal nerves. In these cases, severe pain is felt along the course of these nerves and the overlying skin may at times become anesthetic (anesthesia dolorosa)

Vagus Nerve. Involvement of the vagus nerve may produce dyspnea, dysphagia, vomiting, and bradycardia.

PRESSURE ON RESPIRATORY PASSAGES. *Cough* and *dyspnea* are the commonest symptoms of pressure on the respiratory passages

Cough. This is present in about 60 per cent of these cases, and, in approximately one-half of them, it is the initial symptom Many types of coughs are encountered in cases of aneurysm, the specific type depends upon the underlying cause:

A *dry, rough, and irritating cough* is occasionally associated with wheezing and dyspnea. This type of cough results from pressure on the trachea and main bronchi. Such a cough may increase in intensity and become more troublesome *on exertion*, probably due to the *increase of* pressure caused by distention of the sac of the aneurysm. It tends to diminish *on rest.*

A *productive cough* is present when tracheitis, bronchitis, and bronchiectasis are caused as a result of obstruction.

A brassy and ringing cough suggests involvement of the left recurrent laryngeal nerve and results from pressure on this nerve.

Dyspnea. Dyspnea, the next most frequent symptom of pressure on the respiratory tract, is present in about 40 per cent of these cases, and may often be the initial complaint. It may be caused by (1) diminished intrathoracic space resulting from a large aneurysm, and may appear on exertion; (2) pressure on trachea or bronchus, and then be present even at rest; or (3) reflex irritation of the vagus nerves which might bring about bilateral adductor spasm of vocal cords followed by dyspnea and *stridor*. (4) Occasional paroxysms may be secondary to left ventricular failure resulting from hypertension, aortic insufficiency, or coronary heart disease, and there may be nocturnal dyspnea caused by pressure of the aneurysm on the trachea or bronchus when the patient is in the supine position

PRESSURE ON A BRONCHUS. This causes *pulmonary change* If the pressure is gradual, overdistention of the lung occurs, resulting in emphysema, which occasionally may be mistaken for pneumothorax. Complete obstruction results in atelectasis of the involved lung (Fig. 15-13B), followed by pneumonitis, bronchiectasis (Fig 15-13C), and even fibrosis. This may simulate pulmonary tuberculosis and has therefore been called "aneurysmal phthisis" Atelectasis may involve one or more lobes and is more extensive when the aneurysm involves the descending aorta. Pleural irritation caused by aneurysm of the aorta may give rise to pleural effusion (Fig 15-13D).

PRESSURE ON THE ESOPHAGUS *Dysphagia* is an uncommon manifestation of aneurysm of the aortic arch, but more frequently accompanies aneurysms of the descending aorta. Dysphagia may be caused by various factors:

1 Esophageal spasm resulting from irritation of the left recurrent laryngeal nerve This may occur in the early stages of aneurysm and is transient.

2 Partial obstruction of the esophagus due to compression (Fig 15-13D). This type of dysphagia is usually constant

3 Pain on swallowing, which may be caused by ulceration of the esophagus as a result of pressure

PRESSURE ON BLOOD VESSELS AND HEART. *Superior Vena Cava.* Pressure on the superior vena cava is common in aneurysms of the ascending aorta It produces edema and cyanosis of the head, neck, face, and upper extremities. The superficial veins of the thorax and upper abdomen become dilated and tortuous and fill abnormally in the cephalocaudal direction on the thorax, the reverse being normally true Edema of the right upper half of the chest may at times be produced by unilateral pressure

Pulmonary Artery. This artery may be compressed by an aneurysm of the ascending aorta or aortic arch, giving rise to a clinical picture of *cor pulmonale*

Other Arteries Compression of one or more arteries may lead to *unilateral or bilateral disappearance of the pulse* It might also produce a *delay* in the appearance of the pulse wave, thus the left pulse will be felt later than the right if the aneurysm is located between the origins of the right innominate and left subclavian arteries When *the pulses are markedly unequal*, the blood pressure is also diminished on the side of the feeble pulse A difference of more than 30 mm in the systolic pressure of the upper extremities is highly suggestive of aneurysm.

Veins Compression of large venous channels, e g, the innominate and azygos veins, may occur, producing congestion in the areas drained

Heart The heart is displaced *downward and to the left* in aneurysms of the ascending aorta An aneurysm of the descending thoracic aorta may displace the heart *upwards and to the right*, and pulsation in the epigastric region would then be the presenting sign of the aneurysm.

Physical Signs Due to the Mass. An aneurysm which expands outwards is likely to produce a round expansile mass with a *systolic thrill* A *diastolic shock* may occasionally be present due to the recoil of the blood in the aneurysm The apical impulse might be displaced as already described. There may be a *double pulsation*, the systolic impulse being followed by a diastolic thrust, caused by the recoil of retrocardiac aneurysm (*Hope's sign*).

In cases of aneurysm of the ascending aorta, an area of *dullness* may be detected in the 2d right intercostal space, in the retrosternal area, or below the clavicle. In cases of large aneurysms, *a systolic murmur* is usually present. A *double murmur*, systolic and diastolic, may also be audible, and this may be caused by the blood entering and leaving the aneurysmal sac through a narrow opening. However, in the presence of a diastolic murmur, aortic regurgitation should also be considered. Accentuation of the *aortic 2d sound* is a sign suggestive of aortic aneurysm, but it also occurs per se in syphilitic aortitis

Changes in Circulatory Dynamics. As long as the aneurysmal sac contains fluid blood, it behaves like a large and elastic *reservoir of blood.* As this sac fills during systole, it has a damping effect, and this reduces the systolic pressure and increases the diastolic pressure, bringing it nearer the mean pressure. Hence, the pulse of an artery which takes its origin below the aneurysm will be comparatively feeble and have a slower rise (*pulsus tardus*).

Pulsus tardus always gives the impression of a delayed pulse because the palpating finger feels the peak of the wave and not the onset of the rise, but a real delay may be present. Exact details of the changes in circulatory dynamics are better revealed by pulse tracings.

Some aneurysms with inelastic sacs may behave differently and may rarely increase the amplitude of the pulse distal to the sac.

Although 15 to 30 per cent of aneurysms may be asymptomatic, in *general the important* symptoms of aneurysm are pain, cough, dyspnea, hoarseness, hemoptysis, and dysphagia. The pressure signs and symptoms depend upon the structures compressed

Rupture Syndrome. PERICARDIUM Rupture of an aneurysm of the ascending aorta may occur in the *pericardium*, thus producing *sudden cardiac tamponade* usually resulting in death.

PLEURA AND LUNGS. An aneurysm of the thoracic aorta may rupture into the pleural cavity or a lung. Thus, a sudden fatal *hemothorax* or repeated bouts of *hemoptysis* could occur from the involvement of lung tissue

TRACHEA AND BRONCHI. In *general*, *aneurysms* of the ascending aorta rupture into the

right bronchus, whereas aneurysms of the arch or descending aorta rupture into the left bronchus. Involvement of the trachea is likely to occur in aneurysm of the ascending aorta. *Initially the leak is small and only streaks of blood are coughed up, but often the hemoptysis is profuse and fatal.*

ESOPHAGUS Rupture into the esophagus may occur in aneurysm either of the arch or of the descending aorta. The oozing of blood may be a forerunner of final rupture. Small amounts of blood are frequently vomited; or occult blood is detected in the stools. Because of the vulnerability of these aneurysms, an esophagoscope should be used with great caution, or not at all, on patients who complain of dysphagia

SUPERIOR VENA CAVA. An aneurysm of the ascending aorta may rupture into the superior vena cava The symptoms start suddenly. The face of the patient becomes swollen, cyanotic, and suffused, giving the appearance of strangulation. Other manifestations of superior vena cava syndrome also develop A *continuous thrill and murmur* are detectable in the 1st and 2d right intercostal spaces anteriorly. Congestive failure, with edema of the lower extremities, may develop and the liver may become markedly distended, showing systolic *pulsations* However, the most typical picture is that of cyanosis and edema in the upper part of the body.

INFERIOR VENA CAVA An aneurysm of the *abdominal* aorta may rupture into the inferior vena cava. This leads to sudden appearance of *edema and cyanosis* of the lower extremities, and rectal bleeding *may be present* There may be a *continuous murmur* at the site of rupture. There usually is *evidence of high output failure* with collapsing pulse.

PULMONARY ARTERY. The patient is suddenly seized by an attack of marked dyspnea, and a sense of tightness and fullness *in the chest* *Shock* may supervene, precipitating death, but some patients recover and may live for several months or longer Dyspnea is severe, continuous, and out of proportion to the few *moist* sounds present in the chest The intensity of the dyspnea is probably due to sudden pulmonary congestion. A *continuous thrill and a harsh continuous murmur* are present at the base of the heart, chiefly in the 2d, 3d, and 4th left intercostal spaces, 1 to 3 cm to the left of the sternum. Peripheral signs of wide pulse pressure are manifest, while cyanosis is absent or minimal.

RIGHT ATRIUM OR RIGHT VENTRICLE. Clinical manifestations are similar to those which follow the rupture of an aneurysm of the sinus of Valsalva into the right atrium or right ventricle (see below).

EXTERNAL RUPTURE. Aneurysms of the ascending aorta rarely rupture through the skin. After perforating through the ribs and sternum, an aneurysm may be present as *a mass*, with stretched overlying skin Rupture through the skin is uncommon.

MEDIASTINUM. Rupture into the mediastinum is also very rare.

LOCATIONS

Aneurysms of the Sinus of Valsalva. These are rare and usually due to congenital dilatation, but may be caused by syphilis or bacterial endocarditis.

RIGHT SINUS. As seen on roentgenography or fluoroscopy, an aneurysm in this location produces a round shadow which projects forward and upward to the right, and rests at the root of the aorta on a small base. It often shows intrinsic pulsations as well as mural calcification and may erode the bony structures It may compress the right ventricle and rupture into the right ventricle or atrium, resulting in an aortocardiac fistula. This gives a *continuous machinery murmur* heard behind the sternum It may rupture into the pericardium, resulting in *hemopericardium* and cardiac tamponade.

LEFT SINUS Aneurysms in this location may compress the pulmonary artery and produce cor pulmonale. Rupture of the aneurysm into the pulmonary artery will produce a continuous murmur and simulate patent ductus arteriosus

POSTERIOR SINUS Aneurysms here may rupture into the left atrium and produce an aortocardiac shunt. Aneurysms of the left and posterior sinus of Valsalva frequently escape detection during life because of their position

The Ascending Aorta. The ascending aorta extends upward from the sinus of Valsalva for 5 cm, to a portion just below the innominate artery, its entire course is intrapericardial This is a frequent site for aortic aneurysms Symptoms of aneurysm at this site may be *minimal* even when the aneurysm *is quite* large This is why the early writers (Broad-

bent) called this an "aneurysm of physical signs" The aneurysm may develop towards the right or the left. In those which develop to *the right*, the symptoms may be severe or absent, depending upon the size of the aneurysm The sac develops from the convex surface anteriorly and to the right, giving rise to an *expansile pulsating mass* in the 2d, 3d, or 4th right or left intercostal spaces, or behind the manubrium The pulsation is systolic and often heaving There is associated dullness over the area corresponding to the aneurysm. There may be *a systolic or a diastolic murmur* and quite often a *tracheal tug* is present when the aneurysm extends to the arch of the aorta. The radial pulses are equal If the aneurysm is large, the heart may be displaced to the left Pulsations in the aneurysm will be minimal if it is filled by a thrombus *Cardiac dyspnea* may be present if the patient has left ventricular failure due to aortic incompetence *Precordial pain*, often transmitted to the right arm, *may be felt*. This may be a constant sense of dull retrosternal pain or pressure, which often increases on exertion The electrocardiogram may reveal evidence of left axis deviation, depending upon a frequent coexistence of left ventricular hypertrophy Fluoroscopy may reveal a slight bulge on the right border of the heart at the junction of aorta and right atrium

Aneurysms developing *to the left of the aorta* produce a greater increase in the transverse diameter at the base of the heart and frequently evoke manifestations of right ventricular failure by pressing on the pulmonary artery (*cor pulmonale*) A pulsatile bulge may be present in the 2d, 3d, or 4th left intercostal space The left upper border of the cardiac silhouette appears deformed on fluoroscopy.

The following structures may also be compressed and produce syndromes which have been already discussed right bronchus, lung, and pleura, superior vena cava; pulmonary artery, ribs (with subsequent erosion), sternoclavicular joint.

The pressure manifestations may be progressive and may terminate in rupture of the aneurysm in any of the following sites. pericardium, right bronchus, pleural cavity and lung, pulmonary artery, superior vena cava, or cardiac chambers, or it may rupture outwards. The clinical picture resulting from rupture at each of the sites listed has been already described.

The Arch of the Aorta. Aneurysm of the arch has been called "aneurysm of symptoms" (Broadbent) because its anatomical situation and relation to other organs are such that even a small aneurysm can produce symptoms of compression.

Posteriad to the arch of the aorta lie the trachea, esophagus, sympathetic plexus, and thoracic duct; inferiad, the left bronchus; anteriad, the left phrenic and left recurrent laryngeal nerves. It may come in contact with intercostal nerves or the brachial plexus Pressure on any or all of these structures results in a *compression syndrome*, the manifestations of which have been discussed.

Physical examination may reveal an *abnormal pulsation* at the suprasternal notch or the supraclavicular regions, or both The pulsatile mass may lift the manubrium and later may bulge out (Fig. 15-14A). It is covered by stretched skin, and at times blood may ooze out Though rupture often appears to be imminent, it is uncommon.

Percussion of the manubrium reveals dullness if the aneurysm is large. A rare manifestation is *clubbing of the fingers* on the affected side.

TRACHEAL TUG Owing to the pressure of the aneurysm on the left bronchus, the larynx is drawn downward (*Oliver's sign*) or to the left (*Cardarelli's sign*) with each cardiac pulsation (tracheal tug) If tug is present, it is highly suggestive of an aneurysm of the aortic arch and thus is of help in excluding other mediastinal growths.

The best method of detecting this sign is as follows The patient is kept in an erect position and directed to close his mouth and elevate his chin, thereby stretching the trachea The cricoid cartilage is then grasped between the examiner's index finger and thumb (or palpated by placing the index finger over the Adam's apple) and a gentle and steady upward pressure is applied. If the cricoid cartilage is drawn caudally with each ventricular contraction, then tracheal tug is present. Care must be taken that the fingers are not over the carotid arteries otherwise the transmitted carotid pulsations might mislead the observer

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Last Part of the Arch. In this location, the aneurysmal mass projects backward and can



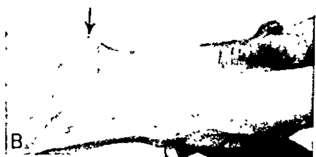


Fig. 15-14. A. Aneurysm of the aortic arch, showing prominent bulge in the region of the manubrium. B. Aneurysm of the abdominal aorta, showing a prominent mass in the epigastric region, as seen in a lateral view.

produce erosion of the second to fourth dorsal vertebrae causing *severe pain* and, infrequently, compression of the spinal cord and consequent *paraplegia*. Among the rarer symptoms, *dysphagia* is the most common. At times, the aneurysm may appear as a bulge between the scapulas and the spine and may attain quite a large size.

The Descending Thoracic Aorta. The thoracic aorta begins at the lower border of the fourth thoracic vertebra, lies in the posterior mediastinum, and extends down to the aortic hiatus, which is located at the lower border of the twelfth thoracic vertebra An aneurysm in this location develops insidiously and is likely to be overlooked till it produces manifestations of compression. *Pain*, the most common symptom, results from pressure on the spine and may be present for 10 to 15 years The site and character of the pain have already been discussed. *Dysphagia, hemoptysis,* and *hematemesis,* though uncommon, are more frequently present with aneurysms in this location than those elsewhere The patient may die suddenly, or present profuse hematemesis for the first time; alternatively the blood may move along the gastrointestinal tract The *clinical picture* depends upon the structures compressed, particularly the left bronchus, left pleura and lung, vertebrae, ribs, spinal cord, and esophagus. *Physical signs* may be conspicuous by their absence, even when the aneurysm assumes large dimensions. However, abnormal dullness on percussion and a systolic pulsation may be observed below the angle of the left scapula or in left interscapular space. When the posterior ribs are eroded, a pulsating mass is seen in the back and, infrequently, when such a mass projects forward an abnormal epigastric pulsation may be present, due to forward displacement of the heart. The femoral pulse may be smaller and delayed as compared to the radial.

DIAGNOSIS Calcification of an aortic aneurysm in this location is frequent and is usually located 1 to 3 mm within the outer border of the aneurysmal shadow; it often extends for a long distance. *Angiocardiography* or *aortography* is of great value in helping to visualize the aorta and, unless the aneurysm is clotted, either one will demarcate the boundaries of the aneurysm.

PROGNOSIS. Fifty per cent of patients with syphilitic aneurysm die because of rupture of the aneurysm. In patients with aneurysm and aortic insufficiency, heart failure accounts for one-third of the deaths Intercurrent infection and asphyxia are responsible for death in some cases About 60 per cent die within 12 months after the appearance of the first symptom Aneurysms of the aortic arch are particularly serious

DIFFERENTIAL DIAGNOSIS Various lesions of the mediastinum may simulate aneurysms very closely Important among them are tumors, e g , carcinoma of the bronchus, thymic tumors, intrathoracic goiter, neurofibroma, lymphoblastoma, and sarcoidosis Some types of cysts, such as dermoid, pericardial, coelomic, and lymphatic, may present diagnostic problems.

A tubercular abscess of the spine and a diaphragmatic hernia will also have to be excluded.

Fluoroscopy will help to determine whether the mass can be separated from the aortic shadow Ingestion of a thin barium suspension will differentiate between intrinsic lesions of the esophagus and compression from outside. Barium studies in the Trendelenburg position will help to exclude a diaphragmatic hernia. It is important to determine whether the shadow lies in the anterior or posterior mediastinum In the anterior mediastinum, a dermoid cyst, a teratoma, a lymphoma, or a lymphangioma is more usual, while tumors of neurogenic origin are located in the posterior mediastinum A dermoid cyst is usually a solitary, round, homogenous opacity in the anterior mediastinum It is sometimes calcified Teratomas often are irregular in density and may contain teeth or bones Lymphatic cysts are generally located in the posterior mediastinum and may be single or multiple A lymphoblastoma will shrink with x-ray radiation

The Abdominal Aorta. Till a decade or two ago, all the aneurysms of the abdominal aorta were considered to be of luetic origin. It is now realized that most of these aneurysms are caused by arteriosclerosis instead

INCIDENCE AND CAUSE Formerly thoracic aneurysms were thought to be seven to ten times more common than abdominal Recently, however, the proportion has declined to 4.1 Current statistics also reflect upon the decline in the luetic origin of these aneurysms and a corresponding increase in atherosclerotic aneurysms

Mamgha et al (1952) found that the ratio of arteriosclerotic to syphilitic aortic aneurysms was 1 10 for each 1,000 autopsies performed during the years 1932–1935 and 1 1 4 in 1940–1948 The ratio decreased thereafter to 1·0 4 (or 2 5 1) in the subsequent group of 1,000 autopsies analyzed for the years 1949–1951.

In the analysis of abdominal aneurysms, 96 per cent were arteriosclerotic and 4 per cent were syphilitic Similarly, in Blackmoore's series (1954) of 124 cases of abdominal aneurysm, 10 were attributed to syphilis Mills and Horton (1938) reported 8.8 per cent of abdominal aneurysms were due to syphilis Atherosclerosis was the cause of 97 out of 102 cases of abdominal aneurysm in the series reported by Estes Congenital defects; abdominal wounds, including gunshot injury; inflammatory vascular lesions due to tuberculosis; streptococcal infection; and rheumatic fever are among the rare causative factors Abdominal aneurysms occur more frequently in men, the ratio being about 5:1. Syphilitic aneurysms usually occur between the fourth and fifth decades, while those of arteriosclerotic origin occur in the sixth and seventh decades.

ASSOCIATED DISEASES Severe coronary arteriosclerosis with myocardial infarction was noted in 16 out of 21 autopsied cases. Angina pectoris, cerebrovascular diseases, pulmonary tuberculosis, and kidney diseases may also be associated with abdominal aneurysm.

SIGNS AND SYMPTOMS. *Aneurysms of the abdominal aorta may be asymptomatic in about one-third of the cases. Syphilitic aneurysms of the abdominal aorta produce symptoms early, arteriosclerotic ones, on the other hand, due to their more anterior location, either are entirely asymptomatic or produce symptoms only at a late stage. Below are the common manifestations, depending upon the location and the size of the aneurysms.

Pain Pain is the commonest symptom, but may be absent in 20 to 50 per cent of cases It may be caused by vertebral erosion, pressure on dorsal nerve roots, hemorrhage into the perirenal space, displacement of a kidney, or ureteric obstruction It is frequently felt in the lumbar region and is paroxysmal at onset, but later becomes constant and boring, throbbing, or cutting The site and radiation of the pain depend upon the location of the aneurysm If the aneurysm involves the upper part of the abdominal aorta, pain may be felt at the epigastrium and may extend over the entire abdomen. If it is located in the lower part of the abdomen, the pain radiates to the lumbar region and may (at times) simulate renal colic in about 20 per cent of the cases It may also radiate down the posterior aspect of the thighs. Root pain radiating from the back to the upper abdomen can also be produced Pain may be so severe as to require opiates It may be modified by change of posture

Pressure Pressure on the spinal cord may give rise to a clinical picture of compression myelitis Pressure on the abdominal viscera,

e.g., pylorus and duodenum, may lead to nausea and vomiting. There may be episodes, simulating paralytic ileus, caused by mechanical compression of the intestine or lesions of the mesenteric arteries. Pressure on the kidney and ureter may produce hydronephrosis.

Pulsation. Some patients are aware of pulsations and may consult a physician about them. Pulsation may occasionally be described by the patient as a throbbing pain, but pulsation and pain may be felt independently of each other.

Physical Signs. The mass is the outstanding physical finding and may be present in the lower epigastric (Fig 15-14B) umbilical, or left hypochondriac regions. In most cases, the mass is pulsatile (*expansile pulsation*) and, in some, it may reveal progressive enlargement. It is worthwhile to emphasize that a pulsating aorta is not diagnostic, because such pulsations may be observed in asthenic individuals with an exaggerated lumbar curve. Neurotic, thin women, particularly, become more conscious of these pulsations. It also must be stressed that the patient should be put in a knee-elbow position to permit the examiner to decide whether the pulsation is from the aneurysm or transmitted from the aorta A *systolic murmur* and a *thrill* have been recorded in only a few cases but this may be partly due to inadequate search for these signs or to intraluminal clotting. The *pulse of the femoral artery may be retarded* and the systolic blood pressure of the femoral artery may be equal to or less than that of the brachial arteries, the reverse being the case normally. However, the diastolic blood pressure may be higher, tending to be nearer the mean pressure. Tenderness is present in about 50 per cent of patients with abdominal aneurysms Although about one-third of the cases may be asymptomatic, the important manifestations of abdominal aneurysm are pain, presence of a pulsating mass in the abdomen, and gastrointestinal disturbances

COURSE AND COMPLICATIONS. An aneurysm of the abdominal aorta may persist for years without causing serious disturbances However, rupture of the aorta, retroperitoneal oozing, obliteration of the lumen by clots (so complete at times as to lead to death), paraplegia from compression of the cord, and obstruction of the superior mesenteric artery, may result

Rupture of the Aorta. This is the chief possible complication. Though an intact aorta can withstand a pressure of 1,000 to 3,000 mm Hg before bursting, an arteriosclerotic aorta may yield to mild hypertension or even normal pressure. Rupture of the aorta is an acute, catastrophic event accompanied by severe pain, in the abdomen or back, which may radiate to the groins or legs. The pain may be of unusual severity, and is described as "agonizing," "piercing," or "tearing;" it is probably not due to the perforation, but to the tearing of retroperitoneal tissues by the blood. Unusual *pallor* may occur early, even before the onset of *shock* which supervenes after a few minutes and may last for hours Some patients *lose consciousness* and die during this stage, but others may survive for a few hours, the so-called "lucid interval." Signs of a gradually increasing retroperitoneal hematoma develop, and paralytic ileus may appear in 5 to 24 hr, with severe distention, vomiting, and hiccup Deaths due to aneurysmal rupture have hitherto been overestimated because these form the bulk of the cases of abdominal aneurysm which are seen at autopsy. *Rupture probably occurs in about 50 per cent of the cases.* An abdominal aneurysm is most likely to rupture into the retroperitoneal space or the peritoneal cavity, and infrequently into the gastrointestinal tract. At times, it may rupture into the inferior vena cava, but rupture through the skin is rare. However, this gloomy picture is changing due to the spectacular results reported by the application of modern surgical techniques Surgical mortality has been said to vary from 10 to 60 per cent. Patients have been operated upon successfully even after rupture. However, it is very important to obtain a correct diagnosis as early as possible.

Retroperitoneal Oozing. Extravasation of blood may precede a major and fatal rupture. This could give rise to new and more severe pains radiating to hips and legs These symptoms may antedate rupture by a few days The retroperitoneal hematomas so produced may assume large dimensions, producing ecchymosis over the lumbar, inguinal, iliac, and scrotal regions and obliterate the psoas muscle shadow on radiography. About 60 to 80 per cent of patients with this difficulty die, but in a rare case there may be survival for long periods

DIAGNOSIS *Roentgenography* is helpful in arriving at the diagnosis of an abdominal aneurysm A *soft shadow* caused by the aneurysm or a large aorta is present in over 50 per cent

of the cases. The most common finding, present in over 70 per cent of the cases, is that of scattered plaques of calcification in the wall of the aneurysm or in the aorta. *Displacement* of neighboring structures or a soft tissue mass may give a hint. Insufflation of colon and stomach with gas, or visualization with a barium meal and descending pyelography, are at times employed to demonstrate displacement and to exclude abnormalities of gastrointestinal and urinary tracts. *Vertebral erosion* is present in a small percentage of cases and occasionally the erosion may involve the ribs at the costovertebral angles Erosion of the spine can be best visualized in the 45° left lateral position With *aortography*, diagnosis can be made with certainty in most of the cases It usually shows a wide lumen of the aneurysm but, at times, the lumen seems relatively normal due to the presence of clots The chief value of aortography lies in (1) determining the extent of aneurysm, particularly with reference to its proximity to renal arteries, (2) visualizing the irregularity of lumen, and (3) demonstrating a normal aorta in a suspected case of abdominal aneurysm *Progressive leucocytosis and anemia*, when associated with fever in the presence of abdominal aneurysm, is highly suggestive of a leaking aneurysm.

PROGNOSIS. In the series reported by Estes, of 102 cases 96 per cent were arteriosclerotic, 1 per cent syphilitic, and rest had a combined causation Only 18 9 per cent of the patients in the series were alive at the end of 5 years In the series reported by Cranley et al, two-thirds of the patients were dead within 3 months after the appearance of symptoms As the mortality resulting from aortic aneurysms is high, the control of aneurysms would add to the longevity of these patients.

DIFFERENTIAL DIAGNOSIS *Correct* clinical diagnosis, confirmed at autopsy or laparatomy, has hitherto been possible in only one-third to one-half of the cases Common conditions which must be excluded include those described below

Renal Disorders The pain produced by abdominal aneurysm has many of the characteristics of renal pain, and therefore is confused with that of nephrolithiasis, perinephric abscess, hypernephroma, hydronephrosis, prostatic urinary obstruction, and pyelonephritis, the pain is rarely relieved by antispasmodics and opiates. These clinical conditions, on the other hand, may simulate an aneurysm. However, infrequently, there is actual involvement of a ureter by an aneurysmal mass A urologic abnormality which cannot be explained should, therefore, lead one to suspect an abdominal aneurysm.

Pancreatic Cysts These may simulate abdominal aneurysm by transmitting the vascular pulsation. Both lesions may displace the stomach anteriorly and show calcification on a roentgenogram.

Intraabdominal Tumors. Tumors, e.g., gastric carcinomas, masses of retroperitoneal lymph nodes, sarcomas, omental tumors, and renal tumors may simulate an aneurysm, especially if they are adjacent to the aorta. Pulsatile tumors, e.g., vascular hypernephromas and tumors of the liver should also be differentiated from aneurysms.

An abdominal mass which shows expansile *pulsations is almost* pathognomonic of an abdominal aneurysm. Tenderness, characteristic of aneurysms, is not associated with the buckling of an arteriosclerotic aorta

TREATMENT

Medical. In the past, rest has been advocated in the expectation that it would induce clotting *Calcium gluconate* also was given for the same purpose. Venesection was performed to reduce the blood pressure, so as to bring about clotting in the aneurysm Potassium iodide is believed by some to relieve pain *Medical treatment of aneurysms of the aorta is unlikely to influence the prognosis.* However, if hypertension is present, limiting physical activity and lowering the blood pressure

cyanosis, and cough, when present, should be treated symptomatically If respiratory stridor is a distressing feature, chloroform inhalation may be useful. In some cases, tracheotomy or intubation of the larynx proves necessary. Complicating congestive cardiac failure and coronary heart disease should receive appropriate treatment.

Surgical (see also Chap. 8). Wiring, acupuncture, galvanopuncture, injection of gelatin into the mass, and production of an arteriovenous fistula have been tried in the past with unsatisfactory results and hence have been abandoned by most surgeons. *Wrapping of the aneurysm in strips of cellophane to bring about periaortic fibrosis has not been too satisfactory. Partial ligation of the aorta* above the aneurysm is of doubtful value. In syphilitic aneurysms the wall of the aorta is generally

firm enough to permit the placement of hemostatic sutures, whereas this is often not possible in arteriosclerotic aneurysms. At present, the treatment of choice in aortic aneurysms, atherosclerotic or syphilitic, is *excision of the aneurysm with graft replacement, if necessary.* The major problem is occlusion of the aorta during the graft replacement. The aorta can be occluded *below* the renal arteries for periods of about an hour, and this is generally adequate for the necessary graft replacement. *Above* the level of the renal arteries, occluding the aorta for more than 20 min at a time is associated with considerable risk. This can be overcome by using one of the following techniques temporary polyethylene shunts; external shunt of large caliber; hypothermia; bypassing the arch of the aorta with the aid of a pump, or using a temporary heterologous shunt between the ascending and the abdominal aorta.

8

Surgical treatment of aneurysms of the aorta

HUSHANG JAVID AND ORMAND C. JULIAN

HISTORY

Interest in the treatment of arterial aneurysm began with Antyllus, a Greek physician who lived in the first century His writings have been lost but their content was preserved by Oribasius, about A D. 350 Antyllus ligated the involved artery proximal and distal to the aneurysm According to a translation quoted by Mahorner, he noted that the operation was dangerous because the ligature could become displaced Though this method of treatment was repeatedly rediscovered and used through the years, notably by John Hunter in treating popliteal aneurysms, it did not contribute to the treatment of aortic aneurysms

A British surgeon named Moore (1864) sought to stimulate thrombosis of aneurysms of the aorta *by threading a long coil of wire into the sac* This method occasionally seemed to be productive of the desired thrombosis, and the principle was reapplied for many years The most recent proponent of this method was Blakemore, who used it until resectional methods of surgery became established This form of treatment could be successful only in *saccular aneurysms* because these are the only ones in which inactivation of the aneurysm cavity is possible and desirable Misuse in fusiform aneurysms was frequent because of a lack of understanding of the pathologic anatomy involved

Dubost et al (1952) resected a large abdominal aneurysm and bridged the defect produced in the aorta with a homologous artery graft. During the interval betwen the performance of this operation by Dubost and its publication, the same type of treatment was applied by Schafer, DeBakey (1955c), and the authors Schafer considered that interruption of blood flow in the infrarenal aorta would be intolerable and added a technique of bridging the site of surgery with a polyethylene tube during the period of occlusion Dubost, DeBakey, and the authors evaluated the situation differently and simply cross-clamped the aorta below the *renal arteries* without producing damage to the temporarily ischemic tissues

Vascular anastomosis and precedent for the implantation of a homologous vascular graft had already been provided. Significant in the development of blood vessel anastomosis was the work of Eck (1879), who first accomplished the union of two blood vessels when he made an anastomosis between the portal vein and the vena cava in the dog Carrel standardized arterial suture technique and provided a firm theoretical and technical foundation for the transplantation of vessels

The most encouraging work in vessel transplantation prior to its use in treating aneurysms was that of Gross (1948), who resected a long coarctation of the thoracic aorta in a young patient and successfully replaced it by a homologous graft. Swan (1950) resected a segment of aorta in a case of coarctation associated with aneurysm and restored the aortic continuity with the graft.

Between 1950 and 1957, surgery of the aorta made rapid progress, and many new problems arising from the extension of this field have been successfully solved. The problem of temporary occlusion of the abdominal aorta was solved when it was proved that occlusion below the origin of the renal arteries could be carried out without damage for almost any necessary time. Temporary occlusion of the thoracic aorta for resection of aneurysm presented two major difficulties: one was the effect of increased vascular resistance upon the heart, the other was the effect of temporary ischemia upon vital organs. The damaging effect of cross-clamping the thoracic aorta has been minimized by the use of various added techniques. General body hypothermia may prevent ischemic changes in the kidney and spinal cord. Shunting blood around the lesion by way of an exteriorized temporary tube passed through a pump has prevented undue cardiac strain Progress in this field has been rapid and rewarding Aneurysms at all levels of the thoracic and abdominal aorta have been successfully resected with varying degrees of danger. Aside from the technical aspects of the actual resection and replacement, important developments have occurred in the graft material used Originally, *homologous arterial tissue* offered a convenient and satisfactory material for grafts. More recently, however, homologous tissue grafts have been almost completely displaced by *prostheses made of various plastic fabrics.*

In the present discussion, the subject of aortic aneurysm has been divided into three sections, namely, abdominal, descending thoracic, and aortic arch aneurysms, each presents its own particular problems.

ANEURYSMS OF THE ABDOMINAL AORTA

The grave prognosis of abdominal aortic aneurysm and the relative ease with which the diagnosis may be made, makes the early recognition and surgical treatment of this lesion extremely important and entirely feasible. The danger of an abdominal aortic aneurysm is well recognized. Estes reported that, of a series of 102 patients with abdominal aneurysm, only 67 per cent survived 1 year after the diagnosis had been made and only 10 per cent were alive at the end of 8 years. These aneurysms were not productive of symptoms at the time of discovery. Once an aneurysm becomes truly symptomatic, the danger of rupture is tremendously increased.

Abdominal aortic aneurysms are almost exclusively *arteriosclerotic* in origin. *Trauma,* which accounts for a number of aneurysms in the thoracic aorta, has not been truly recorded as the causative factor below the diaphragm *Luetic aneurysms* of the abdominal aorta are undoubtedly extremely rare They have not been encountered in the authors' series. Anatomically, arteriosclerotic aneurysms in this region are essentially fusiform in shape and, in the overwhelming majority, the upper end of the aneurysm lies below the renal arteries

The symptomatology of abdominal aortic aneurysm is based on the effect of the expanding lesion on other structures. Small aneurysms rarely produce any symptoms beyond the complaint of pulsation within the abdomen; this may be experienced by thin patients. Compression of the duodenum at the ligament of Treitz and compression and erosion of the paravertebral ligaments and the vertebral bodies produce the major symptoms Occasionally, an aneurysm in this location may produce sufficient compression of one of the ureters to cause hydronephrosis and renal symptoms.

Diagnosis of Abdominal Aneurysms. The diagnosis of an arteriosclerotic abdominal aneurysm depends on physical examination and radiographic findings. Careful abdominal palpation will disclose the pulsating mass which is often tender. Obesity can obscure even moderately large aneurysms. The pulsating mass is usually more prominent to the left of the midline than to the right, and the discovery of an expansile pulse on the lateral border of such a mass is much more diagnostic than anterior pulsation. When lateral expansion during systole cannot be demonstrated, suspicion arises that the pulsation is transmitted and that an intraabdominal tumor, e g., of the pancreas or stomach, may be present. Simple fatty thickening of the mesentery or omentum may produce a sufficient degree of transmission of the aortic pulse to the abdominal wall as to stimulate suspicion of an aneurysm

Posteroanterior and lateral *roentgenograms* of the abdomen, which should be routine in the work-up of older patients, are diagnostic

for aneurysm when they show a layer of *calcification* in its wall. *Aortography* is usually disappointing in proving the diagnosis of aneurysm in suspicious cases This is because the laminated mural clot, which forms in the distended portions of the lesion, maintains a lumen which appears on aortography essentially normal in size, although irregular in shape This same irregularity is observed in patients with atherosclerosis of the aorta without aneurysm In instances in which the physical examination is diagnostic of aneurysm, aortography is neither desirable nor useful. The danger of displacing the mural thrombus within the aneurysm is considerable while, at the same time, the aortogram which might be considered useful for determining the site of origin of the aneurysm in relation to renal artery branches may fail in this objective.

The serious complications of abdominal aortic aneurysm are *rupture* and *massive thrombosis* Thrombosis of an abdominal aortic aneurysm is a rare occurrence, representing a distinct difference from the behavior of *popliteal* artery aneurysms, in which thrombosis is quite frequent On the other hand, *rupture* is the most frequent cause of death in patients with an abdominal aneurysm.

This catastrophe is likely to be announced by severe continuous abdominal and flank pain. The pain is usually referred to the back The common site of rupture is the posterior wall of the aneurysm, where it impinges on the lumbar spine and has been thinned out by constant compression against the bony structure Less frequent points of rupture are directly anterior into the root of mesentery of the small bowel, and occasionally into the duodenum or the inferior vena cava

When rupture occurs in the usual location, *posteriorly*, the immediate bleeding is *into the* retroperitoneal space of the flank and the pelvis Free bleeding into the peritoneal cavity is delayed, and during this period of delay the amount of blood loss is significant and productive of a shocklike state, even though it is limited by the confines of the retroperitoneal tissues This anatomical situation is fortunate in that it provides an opportunity for the diagnosis to be made and the patient to be transported to a suitable facility for resectional therapy of the ruptured aneurysm The period of delay, before extension of the rupture into the peritoneal cavity, may be very brief or may extend up to a 21-day period (observed in one such case in the authors' series).

On physical examination, the patient exhibits a picture of *shock* of varying degree. A usual diagnostic finding consists of transmitted pulsation in the flank and costovertebral angle where the extraperitoneal collection of blood acts like a pulsating hematoma.

Surgical Techniques. Present-day therapy of infrarenal aneurysms of the aorta consists of extirpation of the aneurysm and restoration with a graft of one type or another.

During the early years of this type of surgery the standard graft material consisted of aortic bifurcations recovered at autopsy from patients whose fatal illness did not affect the usefulness of tissues for grafting. Initially, these were taken from the cadaver under operating-room conditions maintaining sterility of the graft by early removal and very careful attention to asepsis. Such grafts were used *in the fresh* state or were preserved by rapid freezing in dry ice or liquid nitrogen to a temperature far below 0°C. The temperature was −70°C in the case of carbon dioxide snow. This method of removal of graft material was so laborious as to increase the difficulty of obtaining it Therefore,

wet, sterilization by application of ethylene oxide fumes, and finally the sterilization of the freeze

clinical experience certain significant disadvantages have appeared in the use of homologous artery transplants. These involve a variety of patient reactions, in which the recipient's tissue may actually react in a form of rejection (Szylayi) Another disadvantage is that the grafted artery tissue is affected by the general tendency of the recipient to store lipoid material in his vessels. This may actually be more pronounced in the graft than in the patient's other arteries. Finally, it has been demonstrated that there is a distinct loss of strength in arterial tissue when it is subjected to ethylene-oxide or beta-propiolactone sterilization The latter substance particularly produces loss of immediate tensile strength and the ability to hold sutures.

Following the work of Blakemore in demonstrating that tubular prostheses of a plastic cloth (Vinyon N) were reliable as replacements for the abdominal aorta, there has been in the past 3 years a decreased use of homologous arteries for replacement of the abdominal aortic bifurcation in favor

TABLE 15-8. ABDOMINAL ANEURYSM, PERTINENT DATA

	Ruptured aneurysm	*Aneurysm treated by elective surgery*
Graft material used:		
Dacron	12	58
Homograft	9	24
Total	21	82
Mortality:		
No cases	9	10
Per cent	43	12

of bifurcations made of plastics. Nylon, Dacron, Orlon, and Teflon have all been tested and have all been satisfactory in varying degrees. Presently, Dacron in a form developed in the author's laboratory and in that of DeBakey and Cooley, as well as nylon in a form developed by Edwards, are in wide use.

Selection of Patients for Surgery. The presence of an abdominal aneurysm is an indication for surgery. Some estimate as to the risk of the operative procedure can be obtained through consideration of several conditions which may be termed "prognostic factors." These factors are (1) age of the patient over 70; (2) the presence of hypertension with a wide pulse pressure; (3) a recent (less than 6 months previously) coronary occlusion, (4) cerebral manifestations of arteriosclerotic disease; and (5) evidence of occlusive arterial disease in the lower extremities In addition to these important factors, it is probably true that obesity increases the hazard of surgery and that nitrogen retention due to renal disease is also a negative factor Table 15-9 indicates the effect of these prognostic factors on the mortality in the authors' series of 103 cases of elective aneurysm resection.

The presence of a number of these factors, however, should not be considered a contraindication for surgery, particularly in the presence of an aneurysm which is either large or symptomatic. This is because of the probability of rupture and death demonstrated by the previously mentioned series.

Preoperative Management. Elective aneurysmectomy should be preceded by a period in which the patient's hydration and cardiac function are brought to the best possible level A significant number of patients have shown some elevation of blood nitrogen due to prostatic hypertrophy, and in these patients a period of bladder decompression is necessary. Digitalization is indicated only if the patient shows heart failure.

The immediate preoperative preparation includes gastrointestinal decompression by continuous suction for a period of several hours, insertion of a urethral catheter in the bladder, and minimal preoperative medication, to prevent depression of respiratory function and blood pressure prior to surgery. Careful cleansing of the lower gastrointestinal tract is accomplished by enemas, never by catharsis.

Experience has proved that vascular anastomoses between major arteries and either homologous grafts or prostheses can be made safely with a single line of fine suture material Attempts to produce an eversion of the vessel ends, in the case of diseased vessels, are likely to fail and in any event are unnecessary. In most cases it is desirable and possible to remove the entire wall of the arteriosclerotic aneurysm. However, in some patients the aneurysm will be so densely adherent to the vena cava as to render its separation from that vessel dangerous In such cases, after removing as much of the total wall as is possible, the inner layers are debrided.

Results of Abdominal Aortic Resection and Graft Replacement. In a small number of cases, resection was performed up to 7 years

TABLE 15-9 EFFECT OF PROGNOSTIC FACTORS* ON MORTALITY IN ELECTIVE RESECTION OF ABDOMINAL ANEURYSM, 82 CASES

Number of factors involved	*Number of patients treated*		
	Total	*Mortality* †	
		Number	*Per cent*
5	3	1	33
4	9	4	44
3	15	4	26
2	38	1	2.6
1	9		
0	8		

* Factors are (1) age over 70, (2) hypertension, (3) myocardial infarct (under 1 year), (4) precordial pain with ECG changes, and (5) obesity.

† Over-all mortality, 12 2 per cent.

prior to the most recent follow-up examination The quantities of cases increase rapidly for periods of time less than 7 years. In the authors' series of 103 aneurysms, the attrition rate from cardiovascular disease and other conditions has been superficially about that which would be expected of patients in this age group The initial mortality rate is presented in Table 15-9

THORACOABDOMINAL ANEURYSMS

Aneurysms of the upper abdominal and lower thoracic aorta fortunately are uncommon The techniques used in their resection take into consideration the danger of producing serious ischemic damage, particularly to the kidneys, but also possibly to liver, adrenal glands, the gastrointestinal tract, and the spinal cord as a consequence of the temporary arrest of blood flow to these organs during the time required to excise the aneurysm and replace it with a graft

The time required for resection and grafting at this level is, of course, greater than would be required for the resection of the infrarenal aorta. This is because two renal artery anastomoses and a reconnection of the superior mesenteric artery and the celiac axis to the graft are required One of the methods developed to overcome this problem consists of the use of *hypothermia* to reduce oxygen demand of the tissues involved. This method, which is entirely adequate for the time required to make two anastomoses for a purely thoracic aneurysm, has not seemed satisfactory in surgery of thoracoabdominal aneurysms.

A second procedure was described by DeBakey It utilizes *a temporary vascular shunt to* conduct blood around the area of partial occlusion while some of the anastomoses are being made This minimizes the period of circulatory arrest to each vascular bed as its artery is handled The authors have used a third method in two cases. *a homologous graft of the thoracoabdominal segment is anastomosed end-to-side to the thoracic aorta above the aneurysm*. This side arm is used for vascularization of all of the visceral branches. As each vital vessel is anastomosed, the blood supply to that organ is reestablished by moving the occluding clamp on the side arm downward below that branch. In this manner, it is possible to reduce the period of temporary occlusion of each of these vessels to about 10 min. After a blood supply is reestablished to the celiac, superior mesenteric, and the two renal arteries through the side-arm graft, the aorta itself may be cross-clamped above and below the aneurysm The diseased segment of aorta is then excised and replaced by a separate graft to restore blood flow to the lower extremities.

Actually, the safe period for temporary occlusion of the visceral branches in the human being is not known Wide variation has been observed in the maximum length of time of vascular occlusion which is tolerated by the kidneys of various species of laboratory animals. Badenoch and Darmody found that rabbit kidney sustains fatal renal damage after 2 hr of renal-artery occlusion. On the other hand, this period of occlusion is well tolerated by the rat kidney. In the rat, a period of occlusion beyond 3 hr causes a 50 *per cent* mortality The dog kidney will tolerate about 2 hr of arterial occlusion with progressive increase in the percentage of mortality after 2 hr. Renal function is temporarily reduced after nonfatal occlusion It gradually returns to normal over a period of 2 to 3 weeks.

Various authors have reported experiences with temporary renal-artery occlusion. Semb noted no significant alteration in renal function after 1½ hr, during which the entire renal pedicle was clamped off while he performed segmental resection of tuberculous portions of kidneys. Bahnson has reported the survival of a patient following occlusion of both renal arteries for 37 min. It is likely that the age of the patient plays a part in the tolerance of renal-artery occlusion and that the arteriosclerotic kidney is much more sensitive.

The tolerance of the liver parenchyma to ischemia has been studied experimentally. The evidence suggests that severe damage approaching fatal change appears after as little as one-half hour of occlusion. There is some [illegible] DeBakey, in his reports on resection of thoracoabdominal aneurysms, produced total hepatic ischemia (except, of course, for portal venous flow) for periods ranging from 44 to 116 min. He observed no instance of disturbance in hepatic function It appears that successful resection of the thoracoabdominal aneurysm may be accomplished

if the period of temporary blockage to the viscera can be kept within safe limits.

ANEURYSMS OF THE DESCENDING THORACIC AORTA

Aneurysms of the descending thoracic aorta arising below the origin of the left subclavian artery are predominantly due to arteriosclerosis but may arise secondary to trauma or syphilitic aortitis In addition, a certain number of fusiform aneurysms in this location are the result of the stabilization of dissecting hematomas of the descending aorta.

As was mentioned earlier, the first method of treatment to receive attention was an attempt to produce *thrombosis of the lumen* of saccular thoracic aneurysms by the introduction of coils of wire. Also in this region, and to some extent in the abdominal aorta, the *wrapping of aneurysms* with some fibrogenic material with the idea of producing scarring was widely used until definitive treatment became available.

Excisional therapy was first applied in the form of *lateral aneurysmectomy* One of the earlier reports by Bahnson (1953) indicated that this method could produce relief of symptoms by excision of the mass whether the aneurysm was in the descending aorta or in some part of the arch. This surgical procedure was not performed many times Several patients who were treated by lateral aneurysmectomy have suffered recurrence of the aneurysm because the remaining portion of the wall of the vessel was weak One such patient was encountered in the authors' series Both of these recurrent aneurysms were resected and the region of the descending aorta replaced by a graft

Resection and graft replacement constitute the ideal method of therapy in that all portions of the aorta which are the site of severe disease may, within limits, be resected Lam and Aram were the first to report excision with graft replacement of an arteriosclerotic aneurysm of the descending thoracic aorta Their patient came to an unfortunate end because of an infection in the aneurysmal sac, which was left behind, but the case and its reporting represented a significant advance in vascular surgery.

The limitation of the amount of aneurysm which may be resected in the descending thoracic area stems from the possibility of interference with the blood supply to the spinal cord. This was actually illustrated by the patient of Lam and Aram, in whom flaccid paraplegia of the lower extremities was noticed until the time of death. In the authors' series, the resection of the entire descending thoracic aorta for aneurysm resulted in fatal damage to the spinal cord. Resection of the thoracic aorta leaving the lower few pairs of intercostal arteries intact is tolerated by the spinal cord without difficulty. Adams and van Geertraden collected from the literature instances of thoracic aortic occlusion for surgery and explained the wide variations in results on the basis of anatomical variations in the blood supply to the spinal cord. It is evident from their study that it is impossible to determine before surgery whether a given length of resection of the thoracic aorta will produce definite cord symptoms.

The second item of importance in the resection of this portion of the aorta arises from the temporary occlusion of blood supply to the organs below the diaphragm. The third consideration consists of the effect on the heart of total cross-clamping of the aorta in this region. These factors and their control through the use of hypotension and hypothermia were reported by the authors (1955). The use of temporary bypasses, from the upper thoracic aorta to a point below the area of resection, provides another method of avoiding complications A similar bypass, energized by a pump, can be made from the left atrium down to an aortic branch such as the femoral artery. This method has been reported by Gerbode and by Cooley, following previous suggestions.

Using one of these methods, resection of the descending thoracic aorta for aneurysm presents relatively little difficulty when one or two distal pairs of intercostal arteries can be left behind. The resection is followed by graft replacement. All of the early resections were done using homologous arteries for the replacement following the early use by Gross and by Swan et al of homologous artery grafts in this region of the aorta. More recently, homologous arteries have in this region, as in almost all others, been superseded by *plastic fabric prostheses*.

Selection of Patients. Indications for resection of thoracic aortic aneurysm are essentially the same for the ascendin[illegible] the arch,

and the descending aorta, because resectional therapy is feasible at all these points.

The symptomatology is almost entirely explainable on the basis of impingement of the aneurysm on other structures. There may be difficulty in swallowing because of compression of the esophagus; voice changes because of disturbance of a recurrent laryngeal nerve; tracheobronchial compression; and severe pain because of erosion of the bony structures of the thorax, principally the vertebral bodies The prognosis in thoracic aneurysm is routinely grave because of the probability of rupture of the aneurysm at a point of compression on bone or some portion of the tracheobronchial tree It is clear that surgical therapy of a thoracic aortic aneurysm is indicated in all cases in which the lesion is discovered, with the limitations imposed by the technical difficulties presented by individual cases Such technical difficulties are rapidly being overcome, with extension of the indications for surgery.

ANEURYSMS OF THE ASCENDING AORTA AND ARCH

Additional technical steps are necessary to permit resection of aneurysms of the arch and the ascending portion of the thoracic aorta. In this region, it is necessary to arrange for a continued blood supply to the cerebral vessels while at the same time the outflow of the heart to major vascular beds in the thorax and abdomen remains unobstructed in order to prevent an unsupportable degree of increase in peripheral resistance

In surgery on the arch of the aorta, this requirement has most frequently been met by the implantation of a suitable *temporary bypass* from the ascending to the descending aorta with the addition of side arms which provide for continued circulation into the carotid arteries. With such a shunt in place, resection of the aneurysm may be accomplished without disturbance of cardiac action or of cerebral flow.

One further requirement must be met for successful surgery on the ascending aorta. This consists of maintenance of coronary-artery flow during the period of occlusion of the aorta just above the heart, or of the necessity to stop the heart for a limited period, thereby making the requirement of coronary flow completely unnecessary.

In lesions confined entirely to the ascending aorta, this problem can be rather simply solved by placing the patient on *total extracorporeal circulation* through pumps and an exterior oxygenator. In the particular use of this equipment, the blood is removed from the circulation from the superior and inferior venae cavae and replaced through a catheter introduced into the femoral artery. The aorta can then be clamped above the heart and below the innominate artery, maintaining coronary circulation by a separate inflow from the perfusion apparatus Studies pointing out the importance of coronary-pulmonary flow seem to indicate that added coronary perfusion under just these circumstances may be unnecessary. This work, which was done in the authors' laboratory, shows the ability of the heart to maintain its own circulation while the remainder of the body is supplied by the extracorporeal pump oxygenator. With this apparatus, the experimental animal can be maintained for long periods, during which some blood must be drained from the coronary-pulmonary circuit at intervals to compensate for bronchial artery flow.

The clinical picture of arteriosclerosis

JEAN LEQUIME AND OLIVIER POLIS

Over the years, human beings ignore what is happening to their blood vessels. The arteries bear the continuous hammering of the arterial pressure; their walls are brushed by the turbulence of the blood and are in contact with the blood, of which the physicochemical properties may change in particular pathological conditions.

When arteriosclerosis begins, this process may assume different clinical forms: Monckeberg's arteriosclerosis, arteriolosclerosis, and atherosclerosis. The pathological aspects that differentiate these three types are related to different causative factors and cause different clinical pictures.

MÖNCKEBERG'S ARTERIOSCLEROSIS

This disease involves the muscular arteries, e.g., the radial, iliac, and intercostal arteries. Subsequent to degenerative phenomena in the media and deposition of calcium salts, the damaged vessel assumes the aspect of a rigid pipe. Even though this type of arteriosclerosis may be regarded as a normal senile process, arterial hypertension favors its development. The caliber of the artery remains unchanged, and consequently there are few symptoms. However, decreased vasomotor activity and reduced blood flow do occur, and, in consequence, increases of systolic pressure and of cardiac work are observed. Subsequently, the sclerosis of the media increases and is often associated with atherosclerosis.

ARTERIOLOSCLEROSIS

This process often involves the preglomerular arterioles of the kidney and the small arteries of the retina. An eosinophilic, amorphous substance accumulates under the endothelium of the arterioles. It has been said that arteriolosclerosis is characteristic of arterial hypertension, but actually it is more a consequence than a cause.

A decrease of the arterial caliber followed by ischemic phenomena is observed. The high peripheral resistance leads to increased diastolic pressure and greater cardiac work.

ATHEROSCLEROSIS

This form is particularly localized in the aorta and the coronary arteries. The lesions are characterized by atheromatous plaques formed by the deposition and accumulation of lipids in the intima plus secondary fibroblastic proliferation. Narrowing of the arterial lumen, caused by the plaques, and thrombosis following their ulceration, explain the symptoms. Sometimes, rupture of the wall occurs and a dissecting aneurysm develops. In general, the destruction of the elastic and muscular layers of the arteries favors dilatation and rupture of the wall, especially if the blood pressure is high.

The *symptoms of arteriosclerosis*, in some cases, appear relatively early. *Diabetes* plays an important role in some cases. In others, *arterial hypertension* seems to be a predispos-

ing factor. While *coronary arteriosclerosis* is more frequent in men than in women below 60 years of age, this predominance is absent in diabetics and decreases in hypertensive patients

Whenever there is evidence of coronary heart disease in young people, familial xanthomatosis and periarteritis nodosa should come under consideration. The *family history* is important in presumed cases of arteriosclerosis. Diabetes, hypertension, xanthomatosis, and the importance of age and sex, have already been mentioned

The *past history*, profession, habits, and other factors should also be carefully discussed Prolonged exposure to cold or humidity might explain vasomotor phenomena, trauma may lead to thrombosis, aneurysms, or vasomotor troubles of the Sudeck type, the role of tobacco has been demonstrated in arteritis of the lower extremities, and certain vascular disorders may follow the use of ergotamine. Thyroid extract, used in hypothyroid patients, may be the cause of precordial pain.

Cardiac Disturbances Due to Atherosclerosis. These are revealed, in some cases, by the clinical picture of heart failure: the patient complains of dyspnea during exertion and orthopnea Also, there is often precordial pain with radiation to the left arm, elicited by exertion and relieved by rest or nitroglycerin. Cold, heavy meals, and unusual exertion favor these attacks. In addition, the classical picture of myocardial infarction may occur.

Atherosclerosis of the Aorta. This condition is frequently asymptomatic, but sometimes, favored by arterial hypertension, a *dissecting aneurysm* may develop This is characterized by severe chest pain, radiating to the back, abdomen, and legs and accompanied by vascular collapse, nausea, dyspnea and, less frequently, dysphagia

Aneurysms. *Abdominal aneurysms*, in contrast with those in the thorax, are generally of atherosclerotic origin. However, those occurring in patients younger than 50 may be syphilitic. These aneurysms may attain a large size and cause various disorders through compression of abdominal organs.

Arteriosclerosis of the Lower Extremities. This form of atherosclerosis causes a typical picture during a walk the patient feels *pain in the calves* that obliges him to stop; the pain is then relieved by a short rest. Such a clinical picture is called *intermittent claudication*. Pain in the legs or cramps in *the calves occurring at night or without exertion*, are evidences of severe ischemia; they sometimes oblige the patient to sleep with his legs dangling out of the bed and are frequently accompanied by *paresthesia*. It should be kept in mind that other conditions may cause similar pain and cramps; coarctation of the aorta and a great number of peripheral vascular diseases are the most common of these. Exposure to cold may cause or favor the symptoms of peripheral ischemia, as proved by the fact that intermittent claudication occurs mostly in the winter. Anemia favors the onset of pain. Even persons with normal peripheral arteries may have pain in the legs if exposed to low *temperatures*

Cerebral Atherosclerosis. In addition to the clinical syndromes of cerebrovascular accidents, cerebral atherosclerosis, due to multiple small lesions, may be accompanied by progressive mental changes: decreases in the intelligence, judgment, and memory, particularly for names and recent events, are common Reminiscing, confabulation, irritability, hostility, egotism, amoral reactions, and even paranoid or demented states, are observed

Arteriolosclerosis of the Kidneys. This is the consequence of chronic arterial hypertension which has dominated the clinical picture for a long time. The patient complains of fatigue, loss of weight, headache, and dyspnea Ankle edema and proteinuria are present. During the evolution of the disease, visual disturbances begin and then epistaxis, itching, digestive troubles, muscular tremors, and cramps are observed. Many patients consulting a doctor for phenomena involving a particular system, reveal, after a complete physical examination, that they are suffering from the results of renal arteriolosclerosis.

DIAGNOSIS

A complete cardiac study is necessary. For instance an aortic stenosis or insufficiency may be the cause of coronary ischemia; left ventricular failure may be either the cause or the result of this ischemia. *Electrocardiograms* in this condition may reveal arrhythmias, conduction disturbances, and changes of repolarization. The exertion and *hypoxia tests* may confirm the diagnosis of coronary insufficiency. A *roent-*

genographic study may reveal enlargement of the heart and dilatation and calcification of the aorta.

The level of blood pressure varies. Arterial blood pressure is frequently normal in atheromatosis of the aorta but may be elevated if there is arteriolosclerosis. Moreover, it should be kept in mind that an increased rigidity of the aorta is followed by some increase of systolic pressure and a decrease of diastolic pressure because the elastic damping of the aortic walls is decreased or absent.

Patients with a *dissecting aneurysm of the aorta* (Chaps. 5 and 6) may present difficult diagnostic problems because the symptoms may simulate those of myocardial infarction, although, on the other hand, a myocardial infarction may occur after the dissection, because of compression of the coronary arteries by the extravasated blood In the differential diagnosis, the persistence of hypertension concurrent with symptoms of shock, sensory and motor difficulties, dysphagia, inequality of the pulses, and sudden onset of aortic insufficiency, are evidence of a dissection The electrocardiogram usually is *not* typical of an infarct

Thoracic aneurysms of atheromatous origin are rare They may be asymptomatic and therefore discovered only through a casual radiographic examination In the case of an *aneurysm of the abdominal aorta,* the x-ray study may show calcification of the wall and vertebral erosion (see Chap 7)

A careful and detailed *examination of the peripheral circulation* is particularly important in arteriosclerotic patients (see Chap 11; also Part 3, Chap 11, The Peripheral Circulation). It should be performed at basal conditions (constant temperature, etc.). Chronic arterial insufficiency may be followed by muscular atrophy of the extremities, chronic infections of the nails, and gangrene Conversely, edema and ulcerations are more frequently due to chronic venous insufficiency than to arterial diseases. Cyanosis is an expression of a slower cutaneous circulation. If the capillary pressure is normal, blanching of the skin, produced by local pressure, should rapidly disappear.

A severe *arterial occlusion* is accompanied by early and diffuse anesthesia, its persistence is of prognostic value. In this condition, elevation of an extremity provokes extreme pallor and lowering it reveals colored spots and slow changes in color. Generally, in an ischemic limb the superficial veins are collapsed and the peripheral venous filling is delayed. A decrease in cutaneous temperature is of particular significance. Palpation, complemented by oscillometry, allows the observer to evaluate the pulsations of the arteries (femoral, popliteal, posterior tibial, and dorsalis pedis). Bilateral absence of the femoral pulses is suggestive of coarctation of the aorta; unilateral absence is generally due to occlusion of the common or external iliac.

Inequality of the femoral pulses may also be due to the presence of an aneurysm

Neurologic signs are frequently found in cerebral arteriosclerosis. It has been stated that the altered vessels may rupture, especially in the presence of arterial hypertension, thus causing a cerebromeningeal hemorrhage However, this concept is being revised and it is now considered that the accumulation of blood is at times caused by thrombosis in an area with rich collateral circulation (*hemorrhagic infarct* of the brain).

The atherosclerotic process narrows the lumen of a vessel causing ischemia and degeneration of the brain tissue. Ulceration of an atheromatous plaque leads to thrombosis of the vessel, but a similar effect may be caused by a sudden drop of blood pressure due to myocardial infarction or other cause. Small arterial lesions, if they are extensive, may also cause various neurologic disturbances Frequent, mild "strokes" followed by moderate neurologic symptoms are observed in such cases. The prognosis is poor and these cases evolve to cachexia and dementia.

Arteriolosclerosis of the kidneys greatly modifies the general condition of the patient The arterial pressure increases, and the diastolic pressure becomes elevated due to the increase in peripheral resistance. As a result, there is hypertrophy of the left ventricle, followed by dilatation of the heart and eventual heart failure.

Examination of the eye grounds reveals exudates, hemorrhages, and papilledema. Anemia is frequent The renal function deteriorates progressively, and this has an important prognostic value proteinuria, hematuria, and nitrogen retention are symptomatic expressions of glomerular damage; tubular injury is shown by renal casts, decreased concentration, and

decreased phenolsulfonphthalein clearance Edema of cardiac or renal origin is frequently present.

Death may be caused by *heart failure* or it may follow a *cerebrovascular attack*. Otherwise, the picture may be that of *uremia:* severe dehydration, anorexia, weakness, disturbances of the electrolyte balance, acidosis with dyspnea and vomiting, hypocalcemia with tetany, secondary hyperparathyroidism with fibrocystic osteitis, convulsions, and hyperpotassemia The latter, which is accompanied by progressive electrocardiographic changes, may cause *ventricular fibrillation* or *standstill* The specific gravity of the patient's urine is usually between 1 008 and 1.012. Ulcerative colitis, diarrhea, and hemorrhages are common

SUMMARY

Some of the clinical aspects of arteriosclerosis have been described. The manifestations usually involve a limited area or a single organ However, it is necessary to remember that these manifestations are related to a diffuse process and that the history and physical examination should be always as complete as possible in order to ascertain the extent of the arterial involvement

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The level of blood pressure varies. Arterial blood pressure is frequently normal in atheromatosis of the aorta but may be elevated if there is arteriolosclerosis. Moreover, it should be kept in mind that an increased rigidity of the aorta is followed by some increase of systolic pressure and a decrease of diastolic pressure because the elastic damping of the aortic walls is decreased or absent.

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phenomenon The latter term is applied in instances in which the clinical manifestations of this disorder are superimposed upon organic vascular disease or may occur subsequent to trauma, Sudeck's atrophy (of bone), or intoxication with ergot or heavy metals.

ACROCYANOSIS The benign nature of this disorder has restricted opportunities for its pathologic investigation Intimal thickening of arterioles and dilatation of capillaries and venules have been noted in the skin of affected parts in some instances (Boas, Lewis and Landis)

LIVEDO RETICULARIS Nonspecific changes consisting of intimal hyperplasia of arterioles, similar to that noted in acrocyanosis, have been described (Barker et al) and may be considered as evidence for the vasospastic nature of this disorder.

ERYTHROMELALGIA (ERYTHRALGIA). There have been no records of pathologic studies which might suggest an organic basis for the clinical findings observed in this disease.

EXPOSURE TO COLD The nature of vascular lesions attributed to environmental cold is variable and dependent upon the severity of exposure In patients with the *pernio syndrome*, changes similar to those observed in Raynaud's disease, livedo reticularis, and acrocyanosis have been described After severe exposure to cold, as noted in *trench* or *immersion foot*, vascular engorgement and thrombosis have been noted early With the onset of gangrene, angiitis simulating thromboangiitis obliterans (Friedman), panniculitis, and hemosiderin deposition in perivascular tissues may be evident Medial fibrosis and intimal thickening of small arteries and veins may also be present (Blackwood; White and Warren) It appears significant that similar changes may be encountered in gangrenous areas regardless of cause, particularly in the presence of secondary infection Block found no changes in the skin obtained by biopsy from trench-foot patients who presented no ischemic manifestations In the author's laboratory, studies of several tissue samples from patients with trench foot and gangrene disclosed only moderate intimal thickening of the small arteries in areas unaffected with gangrene

Arteriosclerosis Obliterans. This term is used to designate arteriosclerosis, occurring in the extremities, which causes occlusion of the lumen either by means of the arteriosclerotic process per se or by thrombosis It constitutes the most common type of occlusive vascular disease of the lower extremities Frequently, both the intimal, or atherosclerotic, type of arteriosclerosis, as well as that characterized by alterations within the media, the so-called *medial, senile,* or *Mönckeberg type of sclerosis* are encountered in affected vessels It should be emphasized that vascular occlusion occurs only rarely in cases of Monckeberg's sclerosis in which atherosclerotic changes are not evident (Silbert et al). Medial, or Monckeberg's, sclerosis has been attributed to vascular degeneration associated with aging or "wear and tear." The causes of atherosclerosis have not been completely elucidated. Nutritional, endocrine, biochemical, and local vascular phenomena, including thrombosis (Duguid) and alterations of intimal ground substance (Rinehart and Greenberg), have been implicated in its pathogenesis

Arteriosclerosis obliterans is most frequently encountered in the distal third of the femoral, iliac, and popliteal arteries, although involvement of the tibial arteries is not uncommon Grossly, affected vessels appear thickened, cordlike and, in some areas, unduly brittle. In those instances in which medial calcification is pronounced, the vessels appear beaded due to the segmental distribution of the lesions The lumen, unlike that in normal arteries, appears to be rigidly held open in cross sections of nonoccluded segments Intimal thickening which may appear yellow or gray, depending upon the amount of lipid present, may also be appreciated. In more severely affected segments, intimal *plaques* may seem to completely obliterate the arterial lumen, a similar effect may be produced by thrombosis. Veins and nerves may appear grossly unaffected, although variable thickening of the former is not infrequent Gangrene, if not complicated by secondary infection, imparts a black mummified appearance to the skin. When gangrene has been complicated by infection, the affected part appears moist and is malodorous, there is considerable sloughing of tissue.

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en [illegible] of the vessel may be disrupted, and the *site* of recent thrombus formation. The intimal change is most often com-

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Pathology of peripheral vascular diseases

EDWIN R. FISHER

Peripheral vascular diseases include the disorders of blood and lymphatic vessels in the extremities and surface regions of the body. Their pathologic aspects are concerned with alterations in the vessels and secondary disturbances in the tissues. The latter are not specific but appear to be dependent upon the degree of vascular occlusion and ischemia produced The similarities of the pathologic findings and the probable pathogenesis of some of these disorders conveniently allow for their consideration as a group Such a presentation is not intended to represent a rigid classification of these diseases, for undoubtedly revisions will become necessary with accumulation of more information

DISEASES OF ARTERIES

Primarily Functional Disorders. Included in this group of peripheral vascular diseases are those disorders in which physiologic and therapeutic considerations indicate the presence of a primary dysfunction of vasomotor activity rather than organic vascular disease However, relatively nonspecific structural changes may occur in severe or protracted instances. Little is known about the gross appearance of affected vessels, and histological studies have been, for the most part, restricted to those instances in which such sequelae as gangrene have become manifest. It has, therefore, become difficult to delineate vascular alterations which might be secondary to disturbances in the tissues from those of the vascular disease *per se*. Significant pathologic lesions have not been observed during the few studies concerned with possible primary alterations of the nervous system. It is to be noted that many of the disorders to be described may appear clinically during the course of other vascular diseases which are organic in nature In such instances, however, pathologic examination usually will allow for identification of the latter.

RAYNAUD'S DISEASE. It is generally agreed that the clinical findings in this disorder are the result of arterial vasospasm rather than organic vascular disease Arteriographic studies performed on patients with Raynaud's disease have failed to disclose evidence of organic vascular occlusion (Allen). Similarly, pathologic studies, although few, have not revealed lesions in the vessels of affected parts in which there were no trophic or ischemic changes. Lewis (1938) clarified the finding of intimal thickening in cases which were unaccompanied by trophic or ischemic changes by noting similar arterial alterations appeared with increasing age in persons without clinical evidence of Raynaud's disease. However, in those instances in which such secondary phenomena have ensued there may be more severe intimal hyperplasia and thrombosis of digital arteries Experimental evidence strongly suggests that such alterations may result from vasospasm or luminal narrowing (Waters and de Suto-Nagy; Williams, 1952). Raynaud's disease is to be differentiated from Raynaud's

TABLE 15-10 DISTINGUISHING MORPHOLOGIC FEATURES OF ARTERIOSCLEROSIS OBLITERANS AND THROMBOANGIITIS OBLITERANS

Portion of vessel involved	*Arteriosclerosis obliterans*	*Thromboangiitis obliterans*
Lumen	Eccentric	Central
Intima	Atheroma and/or hyalinization	Absence of atheroma; proliferation of endothelial cells
Internal elastic lamina	Disrupted	Preserved, contracted
Media	Usually thinned; fibrosis, calcification, ossification	Slight fibroblastic proliferation and inflammatory cells; preservation of muscle
Adventitia	Slight, irregular fibrosis	Marked fibrosis occasionally encircling vein and nerve
Thrombus	Various stages of organization	Cellular, poorly organized

adherent, reddish purple clot may be observed within the lumen of affected arteries and (rarely) veins In later stages the clot becomes yellowish gray. The adventitia is thickened by dense connective tissue which not infrequently *encircles* adjacent veins and nerve segments, making separation of these structures difficult

Prethrombotic lesions of thromboangiitis have not been adequately characterized, from a morphological point of view However, endothelial proliferation may be observed in portions of arteries in which occlusion has not occurred. In those vessels in which the lesion is well developed, the lumen, which remains centrally placed, is occluded by *a thrombus* containing endothelial cells and relatively numerous fibrocytes, as well as some fibrin, erythrocytes, and a few leucocytes (Fig 15-15B). Organization of such thrombi is usually poorly developed. Multinucleated *giant cells* may be observed at the periphery This location of the giant cells represents one morphologic difference between thromboangiitis obliterans and the so-called "giant-cell arteritis" (temporal arteritis). The internal elastic lamina in thromboangiitis obliterans *is unaffected* and may appear contracted and even thickened The musculature of the *media is* well preserved, although varying degrees of fibroblastic, lymphocytic, and neutrophilic infiltration may be noted in this zone. The adventitia is thickened by proliferation of *connective* tissue which, in long-standing cases, encompasses nerve fibers and adjacent veins The [illegible]
canalized
intact, un[illegible]

sence of deformity of the lumen has been considered as representing specific morphologic features of thromboangiitis obliterans (Hall) The distinguishing morphologic features of thromboangiitis obliterans and arteriosclerosis obliterans are presented in Table 15-10.

Ischemic changes, such as gangrene, osteoporosis, panniculitis, muscular atrophy, and demyelinization of peripheral nerves, may also be observed (Fig. 15-16A).

Necrotizing Angiitis, Including So-called Collagen Diseases. The term "necrotizing angiitis" refers to those vascular diseases in which fibrinoid necrosis in most, but *not all* instances, constitutes a salient morphologic feature of their lesions (See also Part 16, Chap. 3) These disorders include polyarteritis *nodosa*, hypersensitivity angiitis, lupus erythematosus, dermatomyositis, scleroderma, rheumatic arteritis, and rheumatoid arteritis All are frequently [illegible]
various [illegible]
vascular [illegible] cardiac involvement and joint manifestations are not uncommon Because of *these* similarities and apparent locus of reaction in the connective tissues of the body, *these* diseases have been designated as "collagen" diseases However, it has not as yet been convincingly demonstrated that the fibrinoid degeneration characteristic of these disorders *is* derived from the amorphous ground substance *rather* than from fibrillary components of the connective tissue including smooth muscle or from the circulating blood. The results of various histochemical (*Fisher* and Baird; *Muirhead* et al) and immuno-

prised of relatively acellular hyaline connective tissue in which small vascular channels are evident. Cholesterol clefts and, occasionally, lipid-laden macrophages, fibrin, hemosiderin deposits, fresh hemorrhages and calcification may also be observed in this zone. The internal elastic lamina is most often destroyed, at least in part. The media appears thinned and is frequently the site of hyalinization, calcification, and even ossification. The adventitia of affected vessels is usually only moderately thickened (Fig. 15-15A). Osteoporosis, atrophy of skeletal muscles, and degeneration of nerve segments may be evident. There do not appear to be any distinctive morphological features to distinguish the arteriosclerosis obliterans which complicates *diabetes mellitus* from that encountered in nondiabetic patients.

Thromboangiitis Obliterans (Buerger's Disease). The nosologic position of this vascular disease has not been conclusively demonstrated Buerger, on the basis of limited experiments, believed it to be caused by an infectious agent. There has been little subsequent evidence to support this contention. The recognition of visceral involvement in rare instances has prompted some investigators to consider thromboangiitis obliterans to be a form of necrotizing angiitis, similar to polyarteritis nodosa and the other disorders classified as "collagen" diseases. However, the predominantly local nature of this disease, as well as the lack of vascular necrosis, represent features perhaps warranting its distinction from the latter. Vasotoxic agents, such as nicotine, have been implicated as causative factors in thromboangiitis obliterans, although it is now generally agreed that this agent represents only an aggravating or accelerating factor. A few reported instances of this disease in siblings have suggested that heredity may play a role in its pathogenesis (Samuels).

Thromboangiitis obliterans is a disease of medium-sized and small arteries and, not infrequently, veins. Its gross and microscopic appearance may vary in the same vessel, depending upon the age of the individual lesions In the early stages of the disease, affected vessels are segmentally contracted, particularly at sites of occlusion. The veins may be similarly involved and, in rare instances, the latter may be the earliest site of involvement. A soft but



Fig. 15-15. A Cross section of femoral artery from patient with *arteriosclerosis obliterans*. The lumen (1) is eccentric and the site of recent thrombosis An older, organized and recanalized thrombus is also present (2). An atheromatous plaque is evident within the intima (3). B Cross section of tibial artery and vein from patient with *Buerger's disease*. The lumen is centrally placed and occluded by a cellular, poorly organized thrombus (1). The internal elastic lamina (2) is intact. The media (3) is slightly hyalinized The adventitia (4) is only moderately thickened in this instance. A thrombus (5) occludes the lumen of the vein.

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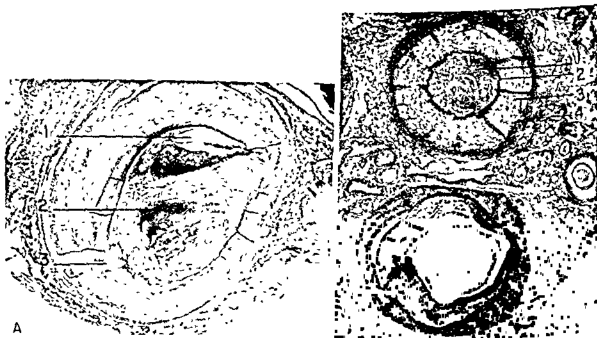


Fig. 15-15. A. Cross section of femoral artery from patient with *arteriosclerosis obliterans*. The lumen (1) is eccentric and the site of recent thrombosis An older, organized and recanalized thrombus is also present (2). An atheromatous plaque is evident within the intima (3). B Cross section of tibial artery and vein from patient with *Buerger's disease* The lumen is centrally placed and occluded by a cellular, poorly organized thrombus (1) The internal elastic lamina (2) is intact. The media (3) is slightly hyalinized The adventitia (4) is only moderately thickened in this instance. A thrombus (5) occludes the lumen of the vein.

adventitia and outer media. The *healed stage* reveals marked adventitial sclerosis The media also is the site of scar formation imparting a ragged appearance to the remaining muscle (Fig 15-17A). The intima is markedly thickened by loose, relatively acellular connective tissue containing moderate amounts of chromotropic substance and small capillaries The lumen is markedly narrowed and may be either central or distorted, depending upon the degree of aneurysmal dilatation Thrombi may be canalized. Phenomena less commonly encountered in polyarteritis nodosa are necrotizing granulomas within the wall and adventitial tissues of the affected vessels (Pagel, E R Fisher). Such nodules may appear in apparently healed vessels and represent exacerbation of the disease. Arterioles and veins are not primarily involved in classical examples of polyarteritis nodosa

HYPERSENSITIVITY ANGIITIS This form of necrotizing angiitis (Zeek et al), unlike polyarteritis nodosa, primarily affects arterioles, capillaries, and venules, and the lesions all appear to be in the same stage of development Microscopically, there is moderate endothelial proliferation accompanied by slight to moderate necrosis of the wall of affected vessels, together with infiltration of neutrophils, lymphocytes, and occasional eosinophils Extravasation of erythrocytes may be evident, thus accounting for *petechiae* The healed stage of these lesions has not been adequately described. It is presumed that healing takes place without significant scar formation

LUPUS ERYTHEMATOSUS There is usually notable variation in the intensity of the vascular damage encountered in this disease, which chiefly affects small arteries and arterioles Fibrinoid degeneration within the media is evident Fibroblastic proliferation is observed in the intima of larger vessels and results in narrowing of the lumen Thrombosis, however, is not observed, and the endothelium usually remains intact. Inflammatory cells are most frequently limited to the adventitia Cellular connective tissue may replace areas of degeneration The arteriolar lesions in the skin do not appear specific More pathognomonic vascular changes may be observed in the central arteries of the spleen, these are characterized by ntitial lamination of collagen Renal lesions



Fig. 15-17. A Cross section of "healed" lesion of *polyarteritis nodosa*, illustrating highly vascularized intima (1) and fibrosis of media (2) and adventitia (3). B Portion of temporal artery, from patient with *temporal or giant-cell arteritis*, revealing fibrosis of intima (1) and foreign-body giant cells (2) in media

consisting of focal or wire-loop alterations of glomerular basement membranes and "hematoxylin bodies" are strongly suggestive, but not diagnostic, of this disease Valvular lesions of the heart, described by Libman and Sacks, may be found in approximately one-third of the cases

DERMATOMYOSITIS The vascular lesions encountered in dermatom...

chemical studies (Gitlin et al.) tend to suggest that perhaps all three components may contribute to the formation of the fibrinoid tissue and that the contribution of each may vary quantitatively depending upon the site of the degeneration, as well as its duration. It is not an uncommon opinion that all these diseases represent a manifestation of hypersensitivity. On the other hand, it has been emphasized that the similar morphologic manifestations of these diseases do not necessarily imply a common originating cause (Klemperer). However, recent immunohistochemical studies of the lesions of polyarteritis nodosa (Mellors and Ortega), lupus erythematosus, rheumatic fever, and rheumatoid arthritis (Vazquez and Dixon) have demonstrated the presence of excess gamma globulin, a finding which is compatible with, though not unequivocal evidence for, such a pathogenesis

Although the distinctions between some of these disorders may appear artificial, certain anatomical, as well as clinical, differences and therapeutic considerations appear to warrant their individual consideration Giant-cell arteritis (*temporal arteritis*), although occasionally considered in this general group of vascular diseases, appears more properly in the discussion of granulomatous forms of vascular disease.

POLYARTERITIS NODOSA. This disease classically involves medium-sized and small arteries. Peripheral manifestations may appear in about 20 per cent of the cases. Grossly affected vessels appear segmentally thickened Frequently, but not invariably, multiple nodules or aneurysms may be evident. This disorder seems to preferentially affect sites of bifurcation Thrombosis with luminal occlusion and gangrene may occur in the extremities.

Microscopically, the disease has been divided into four stages (Arkin), all of which may be evident in the same patient The earliest or *degenerative stage* is characterized by intimal edema and a fibrinous exudate in this layer (Fig. 15-16A). Endothelial proliferation may also be present. Fibrinoid degeneration of the media may be patchy or circumferentially distributed Infiltration of all vascular coats by neutrophils may be observed in the second, or inflammatory, stage During this stage, there is focal disruption of the internal, and occasionally external, elastic laminas, and aneurysmal dilatation may occur. Thrombosis is not infrequent The third, or *reparative, stage* is characterized by fibroblastic proliferation in the



Fig. 15-16 A. Cross section of tibial nerve, from patient with *Buerger's disease*, revealing extreme perineural fibrosis. B. Cross section of small artery of leg from patient with *polyarteritis nodosa* The lesion is considered early with intimal deposition of fibrin (1), slight medial (2) and adventitial (3) inflammation. Necrosis of the media is focal and of mild degree

TABLE 15-11 PATHOLOGIC FEATURES OF NECROTIZING ANGIITIDES, INCLUDING "COLLAGEN" DISEASES

Feature	*Polyarteritis nodosa*	*Hypersensitivity angiitis*	*Lupus erythematosus*	*Dermatomyositis*	*Scleroderma*	*Rheumatic arteritis*	*Rheumatoid arteritis*
Sites of predilection	Any site, G I tract common, usually not lungs, spleen	Any site, common lungs, spleen, usually not G I. tract	Spleen, kidney, skin	Skin, skeletal muscle	Skin, G I. tract, occasionally kidney, heart	Lung, heart, G I tract gonads, kidney	Skeletal muscle, nerve, synovia, rarely heart, G I. tract
Size of vessels	Medium and small arteries	Small arteries, arterioles, capillaries, venules	Small arteries, arterioles	Small arteries, arterioles	Small arteries, arterioles	Large and small arteries, arterioles	Small arteries
Layers involved	All	All	Intima, media	Intima, media	All	All	Adventitia, occasionally all
Necrosis	Marked	Marked	Marked	Rare	Rare	Moderate	Slight
Endothelium	Swollen, proliferation	Swollen	Swollen, proliferation	Proliferation	Proliferation	Slight proliferation	Slight proliferation
Lumen	Eccentric	Central	Central	Central	Central	Central	Central
Thrombus	Frequent	Rare	Rare	Rare	Rare	Rare	Rare
Lamina elastica interna	Damaged	Damaged	Damaged	Damaged	Damaged	Damaged	Damaged
Aneurysms	Yes	No	No	No	No	No	No
Lesions in various stages	Yes	No	Yes	Yes	Yes	Yes	Yes
Infarct	Common	No	No	No	No	Rare	No
Infiltrate	Polys, plasma, lymphs eos (Many)	Polys, lymphs, eos, plasma (Moderate)	Lymphs, polys. (Few)	Lymphs, polys. (Few)	Perivascular lymphs, plasma (Few)	Polys, lymphs, monos, (Many)	Polys, lymphs, monos (Moderate)
Healed stage	Scar, marked in adventitia	Resolution	Slight scar	Slight scar	Sclerosis	Scar, slight, in adventitia	Resolution, slight scar

thrombi Degeneration of the vascular media and lamina elastica interna, as well as hemorrhage into the adventitia, has been noted in experimentally produced arterial embolism (Cosset et al)

Granulomatous Arteritis Syphilitic, tuberculous, and so-called giant-cell or temporal arteritis are all considered to be forms of granulomatous arteritis. However, the exact nosologic position of the latter is not clear Some investigators have considered it to be a form of "collagen disease" Involvement of visceral vessels has been described (Chasnoff and Vorzimer)

SYPHILIS AND TUBERCULOSIS Syphilis or tuberculosis of peripheral arteries is extremely rare The former may assume a gummatous or, more frequently, an endarteritic form characterized by pronounced endothelial proliferation (Moritz) The media appears intact, although the adventitia may be the site of fibrous thickening.

GIANT-CELL ARTERITIS (TEMPORAL ARTERITIS) In giant-cell arteritis, affected vessels grossly appear nodular and thickened Microscopically, there is often pronounced intimal sclerosis, and although thrombosis is unusual it may occur (Fig 15-17B) The internal elastic lamina appears fragmented and the media, particularly its inner portion, is infiltrated with lymphocytes, neutrophils, and plasma cells Macrophages are conspicuous in areas of necrosis Multinucleated giant cells of the foreign-body type are characteristically noted on the medial aspect of the internal elastic lamina and portions of the latter may occasionally be identified in their cytoplasms with appropriate staining techniques Infiltration of lymphocytes and plasma cells may be noted in the adventitia.

DISEASES OF VEINS

Varicose Veins. Varicosities occur most frequently in the long saphenous vein and its tributaries or in other superficial veins of the lower extremities Only rarely are the deep veins involved. Grossly, involved veins appear tortuous, dilated, and thickened, although the wall may appear thin at sites of severe involvement The valves may appear flattened with widening of their commissures, and distal eversion of these structures may occur (Edwards and Edwards) Since ectasia in the spontaneous type of varicose veins is first observed distal to the valves, it is believed that valvular involvement represents a secondary event (Allen et al) The soft tissues of the extremity may be edematous, and ulceration of the skin

tinguishable from those of lupus erythematosus. Involvement of skeletal muscle, however, appears to be more frequently associated with the former. The affected muscles reveal areas of lymphocytic and neutrophil infiltration with necrosis of muscle fibers, as well as other evidence of degenerative change in these structures, notably proliferation of sarcolemmic cells.

SCLERODERMA. In contrast to the lesions characteristic of the preceding two disorders, fibrinoid degeneration of vessels in scleroderma is unusual. More frequently, the vessels of the skin reveal collagenic changes of their walls, together with marked luminal narrowing. Intimal proliferation may also be pronounced. Inflammatory infiltrate is most often absent, although it may be present in early lesions in the adventitia of affected vessels. The corium in well-developed cases demonstrates homogenization, as well as an apparent increase in collagen and corresponding loss of dermal lamina elastica interna. Skin appendages may be obliterated. The epidermis reveals atrophy. Underlying subcutaneous adipose tissue may reveal inflammatory infiltrate and necrosis, fibrosis, and calcification. Ulceration of the digits and gangrene may occur. The lesions in generalized scleroderma are similar in appearance to those encountered in morphea and acrosclerosis (O'Leary and Waisman), the latter representing a localized sclerodermatous process confined to the upper extremities, face, and chest.

RHEUMATOID ARTERITIS. An arteritis affecting small muscular arteries has been described in occasional patients with rheumatoid arthritis (Sokoloff et al., Cruikshank). Although most frequently noted in striated muscle, such vascular involvement may be systemic. The morphologic appearance of the vessels is superficially similar to that noted in polyarteritis nodosa. However, the inflammatory changes appear to be milder and are restricted principally to the adventitia. Aneurysmal dilatation has not been noted and thrombosis is infrequent. Necrosis of the media is often slight.

RHEUMATIC ARTERITIS. Occasionally, patients with rheumatic fever exhibit a disseminated arteritis, principally of large and small arteries, and occasionally of capillaries (von Glahn and Pappenheimer). The endothelium of the involved vessels is usually intact, and thrombosis is rare. The vessel is thickened by a fibrinous exudate into the intima and media. Moderate to marked medial necrosis may also be noted. The internal elastic lamina may be partially destroyed. Neutrophils, lymphocytes, and occasional eosinophils may be observed in the wall and adventitia. The latter also exhibits edema of connective tissue. Healing by scar formation occurs. Periadventitial sclerosis of the degree noted in polyarteritis nodosa, however, is usually not encountered.

The characteristic features of the various necrotizing angiitides and collagen diseases which may affect the extremities are tabulated in Table 15-11.

Arterial Thrombosis and Embolism. Thrombosis is a frequent finding in arteries affected with arteriosclerosis obliterans or thromboangiitis obliterans. In the absence of antecedent vascular disease, such an event may occur during the course of various infectious diseases; in blood dyscrasias, particularly polycythemia vera; in severe heart failure; and following either acute or chronic trauma. The appearance of the thrombi is similar to that noted in thrombosis of veins. Microscopically, in the primary form, there is little if any inflammatory response noted in the wall of affected vessels. However, when thrombosis results from trauma reactive changes may be conspicuous, although even these changes may include no apparent alteration of the adventitia or wall of the vessel. In this instance, *thrombosis* apparently results from damage to the endothelium caused by transmission of the traumatizing force to this vascular layer (Anderson).

Emboli in the peripheral vessels are most frequently derived from thrombi formed within the heart during episodes of atrial fibrillation or following myocardial infarction or endocarditis. Less frequent sites of origin for emboli are thrombi in aortic aneurysms or on the surface of arteriosclerotic aortic plaques. Thrombi within pulmonary veins or in peripheral veins rarely give rise to arterial embolism. This only occurs when a patent foramen ovale is present, and such a phenomenon is called *paradoxical embolism*. Morphological distinction of emboli from thrombi is often impossible once organization has begun. However, at early stages emboli may appear with little or none of the marginal organization characteristic of

TABLE 15-11. PATHOLOGIC FEATURES OF NECROTIZING ANGIITIDES, INCLUDING "COLLAGEN" DISEASES

Feature	*Polyarteritis nodosa*	*Hypersensitivity angiitis*	*Lupus erythematosus*	*Dermatomyositis*	*Scleroderma*	*Rheumatic arteritis*	*Rheumatoid arteritis*
Sites of predilection	Any site, G.I. tract common, usually not lungs, spleen	Any site, common lungs, spleen, usually not G.I. tract	Spleen, kidney, skin	Skin, skeletal muscle	Skin, G.I. tract, occasionally kidney, heart	Lung, heart, G.I. tract, gonads, kidney	Skeletal muscle, nerve, synovia, rarely heart, G.I. tract
Size of vessels	Medium and small arteries	Small arteries, arterioles, capillaries, venules	Small arteries, arterioles	Small arteries, arterioles	Small arteries, arterioles	Large and small arteries, arterioles	Small arteries
Layers involved	All	All	Intima, media	Intima, media	All	All	Adventitia, occasionally all
Necrosis	Marked	Marked	Marked	Rare	Rare	Moderate	Slight
Endothelium	Swollen, proliferation	Swollen	Swollen, proliferation	Proliferation	Proliferation	Slight proliferation	Slight proliferation
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Thrombus	Frequent	Rare	Rare	Rare	Rare	Rare	Rare
Lamina elastica interna	Damaged	Damaged	Damaged	Damaged	Damaged	Damaged	Damaged
Aneurysms	Yes	No	No	No	No	No	No
Lesions in various stages	Yes	No	Yes	Yes	Yes	Yes	Yes
Infarct	Common	No	No	No	No	Rare	No
Infiltrate	Polys., plasma, lymphs., eos. (Many)	Polys., lymphs., eos., plasma (Moderate)	Lymphs., polys. (Few)	Lymphs., polys. (Few)	Perivascular lymphs., plasma (Few)	Polys., lymphs., monos. (Many)	Polys., lymphs., monos. (Moderate)
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thrombi. Degeneration of the vascular media and lamina elastica interna, as well as hemorrhage into the adventitia, has been noted in experimentally produced arterial embolism (Gosset et al.).

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GIANT-CELL ARTERITIS (TEMPORAL ARTERITIS). In giant-cell arteritis, affected vessels grossly appear nodular and thickened. Microscopically, there is often pronounced intimal sclerosis, and although thrombosis is unusual it may occur (Fig. 15-17B). The internal elastic lamina appears fragmented and the media, particularly its inner portion, is infiltrated with lymphocytes, neutrophils, and plasma cells. Macrophages are conspicuous in areas of necrosis. Multinucleated giant cells of the foreign-body type are characteristically noted on the medial aspect of the internal elastic lamina and portions of the latter may occasionally be identified in their cytoplasms with appropriate staining techniques. Infiltration of lymphocytes and plasma cells may be noted in the adventitia.

DISEASES OF VEINS

Varicose Veins. Varicosities occur most frequently in the long saphenous vein and its tributaries or in other superficial veins of the lower extremities. Only rarely are the deep veins involved. Grossly, involved veins appear tortuous, dilated, and thickened, although the wall may appear thin at sites of severe involvement. The valves may appear flattened with widening of their commissures, and distal eversion of these structures may occur (Edwards and Edwards). Since ectasia in the spontaneous type of varicose veins is first observed distal to the valves, it is believed that valvular involvement represents a secondary event (Allen et al.). The soft tissues of the extremity may be edematous, and ulceration of the skin

or stasis dermatitis may complicate protracted cases.

Microscopically, there is frequently hypertrophy of medial musculature, although in some segments the wall may appear thinned and fibrotic. The lamina elastica interna may appear normal. In areas where there is medial fibrosis, the fibers may be disrupted or absent. The intima is frequently the site of moderate sclerosis characterized by eccentric deposition of relatively acellular hyaline connective tissue. Thrombosis is occasionally noted.

Thrombophlebitis and Phlebothrombosis. Although it is not uncommon to observe a certain degree of inflammatory change within veins occluded by thrombi, the distinction between thrombophlebitis, in which this change is pronounced, and phlebothrombosis, a more bland lesion, appears warranted (Ochsner and DeBakey) The former may result from infection, or chemically or physically induced trauma, whereas in phlebothrombosis such inciting agents are not evident Stasis, alterations in endothelial cells, and alteration of the chemical and physical properties of the blood, factors considered essential for thrombus formation, may or may not be apparently operative in all instances of phlebothrombosis. The type of venous thrombosis (in the extremities) which may accompany some mucin-secreting carcinomas, particularly those of the pancreas, lung, or gallbladder, resembles other instances of phlebothrombosis (Fisher and Baird). The exact nature of this association has not been clearly elucidated

The gross appearance of affected veins will vary depending upon the degree of inflammation, as well as the duration of the pathologic changes. In thrombophlebitis, the vein appears thickened and edematous, in phlebothrombosis it may appear relatively normal. The *luminal thrombus* at the site of occlusion in thrombophlebitis is characteristically adherent to the lining of the vessel but, in phlebothrombosis (at least early in its course), it may be removed with greater ease. These observations indicate a relationship with the more frequent occurrence of *pulmonary emboli* in the latter In both instances, the color of the thrombus at its initial site of formation depends upon the relative quantities of platelets, fibrin, leucocytes, and erythrocytes. Those thrombi in which the last are abundant appear red as opposed to the gray color of clots comprised principally of platelets and fibrin. The *lines of Zahn*, characteristic of ante-mortem thrombi, may be frequently observed. Propagation of the thrombus in the form of a red "tail" usually occurs proximally in the direction of the circulation. "Tail" formation appears to be more frequent in phlebothrombosis, and the thrombi removed from the veins or pulmonary artery following embolization frequently appear as casts of the vein of origin and its tributaries The vein may appear cordlike after recovery from thrombophlebitis. The lumen in both forms of venous thrombosis may be either partially or completely occluded, depending upon the degree of organization and canalization of the preexisting thrombus.

Microscopically, the *thrombus* is observed to be comprised of varying proportions of laminated masses of fibrin and platelets separating leucocytes and erythrocytes. Organization proceeds from the periphery of the clot; it is characterized by the proliferation of fibroblasts and newly formed capillaries. The end result of this process is a fibrous plaque containing vascular spaces of varying size. The luminal surface of incompletely occluding thrombi may be covered by regenerated endothelial cells The walls of thrombophlebitic veins reveal edema and marked inflammatory infiltration as well as fibroblastic proliferation. On the other hand, only mild inflammatory change is observed in phlebothrombosis, and this is usually confined to the inner medial and intimal coats The adventitia and surrounding tissue are also frequently affected by inflammation in thrombophlebitis.

Phlebosclerosis. Focal intimal sclerosis is not infrequently encountered in the veins of elderly persons. Similar changes have also been noted in the popliteal veins of newborn infants (Lev and Saphir) and is considered by some authors (Hauswirth and Eisenberg) to comprise a distinct entity in young persons The origin and pathogenesis of *phlebosclerosis* have not been defined and it is unlikely that such a lesion is clinically significant Phlebosclerotic changes are unlike the atherosclerotic changes in arteries, since lipid deposits and calcification are not observed Scott recently demonstrated the similarity between this intimal change and that observed following the organization of thrombi and has suggested that

many cases may be the result of this process. Grossly, involved veins are narrow and their lumens variably compensated. Complete occlusion is unusual. Microscopically, the lumen appears to be narrowed by flat or protuberant deposits of relatively acellular connective tissue containing moderate amounts of chromotropic substance On occasion, small capillary spaces and moderate fibroblastic proliferation may be noted Hemosiderin deposits are variable Similar intimal changes are not unusual in varicose veins The wall may appear unaffected or be thin as the result of fibrosis

DISEASES OF LYMPHATICS

The swelling of soft tissues resulting from an excessive accumulation of lymph (*lymphedema*) may be the result of inflammatory or noninflammatory disorders affecting the lymphatic vessels. Noninflammatory lymphedema appearing spontaneously in the lower extremities of young girls between the ages of 9 and 25 has been designated as lymphedema precox It was the most frequent form of lymphedema encountered in 300 cases of this condition by Allen et al Congenital lymphedema, also noninflammatory, may be hereditary, in which instance it is referred to as *Milroy's disease* (Milroy) The swelling of an extremity resulting from the obstruction of lymphatics and nodes by metastatic tumors or postirradiation fibrosis, and that following resection of lymphatic structures (as in the treatment of malignant neoplasms) are also of the noninflammatory type Lymphangitis, filariasis, or local injury is responsible for the vast majority of inflammatory forms of lymphedema.

In congenital [illegible] sues [illegible] a rela[illegible]tion is most conspicuous about the deep fascia A decrease of fatty tissue in the affected part is notable.

The microscopic appearance of congenital edema has been considered characteristic and distinct from other forms (Mason and Allen) Replacement *of much* of the adipose tissue by markedly dilated or telangiectatic lymph spaces containing a simple endothelial lining is outstanding These channels are separated by loosely formed connective tissue The corium of the overlying skin is thickened Evidence of inflammation or alterations of blood vessels is absent. On the other hand, in inflammatory forms of lymphedema, many of the lymphatic vessels may contain thrombi or be occluded as a result of the inflammatory process. Angitis and fibrosis of the supporting tissues may also be apparent.

TUMORS OF PERIPHERAL VESSELS

The multiplicity of terms utilized in the nomenclature of tumors of blood and lymphatic vessels has resulted in much confusion concerning their classification. Furthermore, there is often great difficulty in distinguishing those tumors considered to be true neoplasms from hamartomatous growths, malformations, and simple ectasias. The following classification, although perhaps oversimplified, appears to be of practical value. The gross *appearance of tumors* of peripheral vessels is highly variable and is largely dependent on the number of vascular channels present and their structure: they are red, purple or blue, as well as pale or colorless. They may or may not be compressible, their growth may be circumscribed or diffuse, furthermore, encapsulation is uncommon

Blood Vessels. HEMANGIOMA The typical hemangioma is a benign, circumscribed, unencapsulated neoplasm consisting of blood vessels formed by vascular channels lined with a single layer of normal-appearing endothelial cells, and having a delicate wall *comprised* principally of reticulum fibers Adventitial cells *may* also be somewhat *conspicuous and newly formed* vascular buds may be recognized Those tumors in which *the vascular* spaces are small and slitlike have been *referred* to as *capillary hemangiomas*, whereas those characterized by large channels are described as *cavernous forms* Such *lesions are* frequently congenital. The *sclerosing hemangioma* is characterized by relatively occult vascular *channels with* a simple endothelial lining surrounded by curlicues of dense *collagen* Foam cells, as well as *hemosiderin-laden* macrophages, may be observed *in the* stroma.

HEMANGIOENDOTHELIOMA. This term is reserved for those tumors in which there is a neoplastic proliferation of endothelial cells *Occasionally*, the lumens may exhibit papillary formation. *Such lesions* are usually slow-growing and may metastasize *relatively late in* their development.

HEMANGIOPERICYTOMA. Evidence suggests that this neoplasm arises from the adventitial pericytes of vascular channels (Stout and Murray; Fisher et al.). Not infrequently such spaces are occult with routine staining techniques, but are well demonstrated by reticulum methods which also reveal the extravaginal position of the tumor cells. The latter most frequently are spindle-shaped, with a whorled distribution about the vascular spaces. Groups of tumor cells are separated by varying quantities of stromal connective tissue Metastases have been observed in about one-third of the patients in one series (McCormack and Gallivan), and isolated reports of such behavior have not been infrequent. There seem to be no histologic characteristics which would enable one to predict such an event.

GLOMUS TUMOR. This tumor represents another vascular neoplasm derived from pericytes, most often at sites where normally there are small arteriovenous shunts, the *Sucquet-Hoyer canals* However, they also have been noted in such sites as the stomach where such structures are not evident (Kay et al). Morphologically, typical examples exhibit adenomatoid formations of rounded perithelial cells Nonmedullated nerve fibers may also be identified. A reticulum stain reveals fibers surrounding individual cells, whereas, in hemangiopericytoma, reticular cells are distributed about groups of tumor cells Such lesions are frequently, but not invariably, exquisitely tender They are benign.

ANGIOSARCOMA The term "angiosarcoma" is commonly utilized in reference to all malignant tumors of vascular origin The author has reserved this term for those lesions resembling fibrosarcomas in which the tumor cells tend to form vascular spaces Such neoplasms are rare It is apparent that, in many instances, differentiation from a highly vascularized fibrosarcoma may be impossible. Their behavior appears to be similar to that of other sarcomas

KAPOSI'S SARCOMA. Kaposi's sarcoma is that form of vascular neoplasm characterized by a variable histological picture apparent not only in different sites but in a single lesion In (perhaps) the early phase it appears as a simple hemangioma associated with intervascular collections of hemosiderin-laden macrophages and histiocytes and a few lymphocytes Later, hemangioendotheliomatous areas, as well as fibrosarcomatous or true angiosarcomatous elements, become evident. It is as yet not clear whether the multiple lesions observed in many instances represent true metastases or autochthonous growths. Lymphedema, apparently resulting from lymphatic obstruction, is not uncommon in the extremities

HAMARTOMAS. This term refers to those vascular tumors in which smooth-muscle elements can be identified within the wall of the component vessels. Certain vascular anomalies with a distinct clinical picture have also been considered hamartomatous (Landing and Farber). These include the syndromes of angiomas of the face and ipsilateral cerebral cortex (Sturge-Weber), cerebellar, retinal, and visceral angiomas with adenomas of the kidney and hepatic and pancreatic cysts (Lindau-von Hippel), and angiomas with dyschondroplasia (Maffucci) Morphologically, the latter contain both hemangiomatous and hemangioendothelial components.

MALFORMATIONS. Included in this category are the various arteriovenous fistulis or aneurysms In the extremities, these are frequently traumatic in origin. The venous segment reveals marked intimal thickening

Lymphatic Vessels. LYMPHANGIOMA, LYMPHANGIOENDOTHELIOMA, AND LYMPHANGIOPERICYTOMA These are the lymphatic counterparts of similar neoplasms of blood vessels. Their distinction from the latter is largely based on the absence of erythrocytes within the vascular compartments.

POSTMASTECTOMY LYMPHANGIOSARCOMA Six cases of this unusual vascular lesion were first reported by Stewart and Treves (1948) as a complication of postmastectomy lymphedema Since then, 20 cases have been recorded (Hermann and Gruhn). Metastases are not infrequent. Morphologically, the lesions are similar in appearance to those of Kaposi's sarcoma, particularly the hemangioendotheliomatous components of this form of vascular neoplasm

11

Clinical aspects of peripheral vascular diseases

DAVID I. ABRAMSON

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

Thromboangiitis obliterans is a generalized vascular disorder with the predominant changes occurring in the extremities It primarily affects young men and is characterized by remissions and exacerbations Whereas at one time it was believed that the disease affected only Jews of Slavic extraction, this view is no longer accepted For example, a recent study of the incidence of thromboangiitis obliterans in a vascular center set up by the Army during World War II revealed that Jews made up only 8 3 per cent of the series (Abramson)

Causes No causative agent has been established, although several have been proposed. Among them are the ingestion of bread made of grain containing ergot as a contaminant, dermatophytosis, and typhus fever Tobacco smoking has also been implicated and, in the view of some workers (Silbert), it is the principal if not the sole cause of the disease.

Clinical Picture and Course. VENOUS INVOLVEMENT In about 40 per cent of cases, the early state of thromboangiitis obliterans is characterized by pathologic alterations in the superficial veins, producing segmental thrombosis. Because of the fleeting character of the process and because of the unpredictable manner in which it travels from segment to segment of the same and different vessels, it has been given the name of *superficial migratory thrombophlebitis*. Veins of several limbs may be affected simultaneously. Despite the widespread response in the extremities, the condition is not associated with any systemic changes Eventually the phlebitic process may disappear and be replaced by signs of arterial impairment, or both may be present at the same time.

ARTERIAL INVOLVEMENT. During the early stage of pathologic changes in the arterial tree, a diagnosis of thromboangiitis obliterans may be difficult to make The complaints generally consist of *vague pains* in the muscles of the calf or foot, produced by walking long distances and disappearing soon after the patient rests (*mild intermittent claudication*). The associated objective findings are also minimal. The pulsations in the main vessels of the extremities are readily palpable, although there may be a slight decrease in amplitude of one or more, as compared with the arteries on the opposite normal side The various tests for arterial insufficiency are usually too gross to be of value in determining the presence of an impaired arterial circulation.

As the occlusive process advances, the clinical picture comes into better focus Clear-cut *intermittent claudication* is now experienced in one or both lower extremities on walking relatively shorter distances, although symptoms are generally not present at rest. *Pulsations are definitely reduced in one or several peripheral*

arteries, and this finding is confirmed by decreased oscillometric readings, at least for the lower portion of the leg. Slightly abnormal color changes and a lowered skin temperature may also be noted

Further progression of the disease is manifested by the appearance of *rest pain* due to an associated ischemic neuritis. At this stage, the claudication distance may have fallen to as low as one-half of the average city block. A more marked reduction or even absence of pulsations may now be present, associated with decreased or absent oscillometric readings at the various levels on the leg and thigh. Invariably a positive plantar pallor test and a delayed venous filling time (Part 3, Chap 11, The Peripheral Circulation) can be elicited in the involved limb.

Finally, as the circulation to the skin becomes insufficient to take care of its metabolic needs even at rest, slight trauma may be enough to initiate trophic disturbances, such as an *ulcer* or *gangrene* (Fig. 15-18); lesions may also arise spontaneously. Secondary infection may occur, although this is not as frequent as in the case of arteriosclerosis obliterans No difficulty should be encountered in making the diagnosis at this stage since signs of a very severe degree of arterial impairment are obvious.

Prognosis. Provided the pathologic process in thromboangiitis obliterans is limited to the blood vessels in the extremities, and the relatively rare involvement of the arteries of the heart and brain has not occurred, the prognosis as to life is good. However, portions of limbs or entire limbs may be lost if the patient does not abide by the proper therapeutic regimen. On the other hand, if he follows medical instructions, he will probably live a normal life span without the appearance of nutritional disturbances, although his physical activity will be limited by the severity of the intermittent claudication.

Treatment. ABSTINENCE FROM SMOKING The most important single therapeutic approach in thromboangiitis obliterans is *abstinence from smoking*. If the patient cooperates in this regard, it is a good possibility that there will be no further progression of the obliterative process and that the symptoms will become less severe as a result of the simultaneous and unimpeded growth of collateral circulation On the other hand, if smoking is continued, even though markedly reduced, almost invariably there will be an exaggeration of complaints and an increased probability of developing ulcerations and gangrene

PHYSICAL ACTIVITY. The question always arises as to how much exercise the patient with thromboangiitis obliterans should be permitted to do In general it can be stated that, if he is free of nutritional disturbances, he should be advised to determine the range of effort that is possible without producing intermittent claudication and to stay within it. However, some workers believe that graded exercises are of value because of the possibility that the load placed on the vascular tree in the affected extremity will act as a stimulus for further

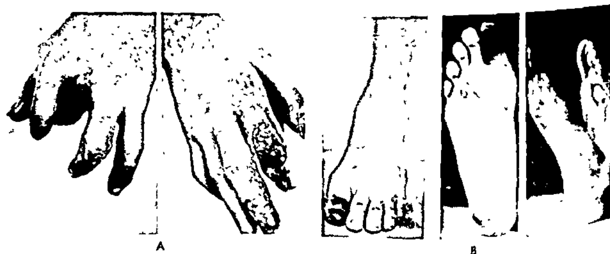


Fig. 15-18. Trophic changes in thromboangiitis obliterans. A. Ulceration and gangrene of fingers, with previous amputation of one digit. B. Gangrene of great toe.

growth of collateral vessels. In any event, at no time should the patient continue to walk after the pain has become severe; otherwise, irreversible changes might occur in the involved muscles. A life of physical inactivity should be discouraged, since it may lead to disuse atrophy of the muscles of the lower extremities, producing further impairment of walking, and also mental deterioration and the adoption of the role of an incurable invalid. It is necessary to point out to the patient that the onset of intermittent claudication involves no serious consequences, the pain acting merely as a deterrent to further physical activity.

In order to increase his walking distance, the patient should attempt certain simple procedures. He will soon learn that, if he reduces his usual pace considerably, he will be able to cover much more ground before having to stop as a result of the pain. Some individuals find the use of a cane efficacious, since by this means the weight placed on the involved extremity is reduced. Others learn that, if they walk stiff-legged without bending their knees or using their calf muscles to any degree, walking distance will also be prolonged.

LOCAL CARE OF THE EXTREMITIES. Of great importance in the prevention of nutritional disturbances is the proper local care of the limbs. This involves a detailed explanation by the physician of the various measures that the patient must take, as well as a discussion of the possible serious consequences of their neglect. A printed or mimeographed list of directions, such as is presented below, may help remind the patient of his role in the therapeutic regimen.

Local hygiene and protection of the limbs are important points to emphasize. The feet should be washed daily with lukewarm water and soap and thoroughly dried, especially between the toes, since moisture at these sites may be responsible for the appearance of a fungus infection. It is advisable to keep the skin of the foot, particularly that of the heel, soft by the use of some type of lotion containing a lanolin base.

Since cold is a very potent vasoconstricting stimulus, it is necessary to reduce exposure of the extremities to this agent as much as possible. In the winter months, the patient should wear woolen socks and full-length woolen drawers. The rest of his body should be kept warm, in order to prevent reflex vasoconstriction in the feet.

Another very important point is the protection of the affected extremity from injury. If his work involves exposure to trauma, it is advisable for the patient to change his job. He should always wear shoes that are well constructed and of the proper size, in order to prevent the formation of blisters. Some type of metal covering on the tip of the shoe may be useful in protecting the toes from possible injury. The toenails should be trimmed carefully and not too closely, and the sides of the nails should not be touched.

The treatment of ingrowing toenails, corns, callouses, and bunions should not be attempted by the patient, but should be carried out by a physician or chiropodist who is acquainted with the fact that a *reduced local* blood flow exists. Even slight abrasions, blisters, or burns should receive special *consideration*, and the ordinary type of antiseptic, e.g., *tincture of iodine* or Mercurochrome, should *not* be used in their treatment. For the same *reason*, any type of corn plaster is contraindicated. Fungus infections should be treated immediately and thoroughly, using mild fungicides, such as a combination of zinc undecylenate, undecylenic acid, and talcum (*Desenex*), 10 per cent undecylenic acid (*Timofax*), propionates and caprylate compound (*Sopronol*), and Asterol dihydrochloride.

TREATMENT OF ISCHEMIC NEURITIS. Therapy in the control of ischemic neuritis is generally *not very effective*. This is especially true for the shooting pains and paresthesias *experienced* when the patient prepares for sleep. Nevertheless it is worthwhile to give *vitamin* B_{12} a clinical trial, using intramuscular injections of 50 or 60 µg two or three times a week. Large doses of thiamine chloride by mouth (200 mg three or four times a day) and the intramuscular injection of crude liver extract may also be of value.

SYMPATHECTOMY. The role of sympathectomy as a therapeutic agent in thromboangiitis obliterans has *not* been established. There is considerable physiological and clinical evidence to support the *view that this* procedure is of little (if any) use in increasing claudication distance, and hence it *should* not be utilized for such a purpose alone. Whether or not

sympathectomy acts to prevent the appearance of nutritional disturbances cannot be determined on the basis of available evidence. Its use in the presence of an ulcer or gangrene is discussed below.

TREATMENT OF ULCERATIVE OR GANGRENOUS LESIONS. *Control of Infection.* In the presence of a nutritional disturbance, it is essential first to control any secondary infection, since otherwise progression of the lesion will occur, due to further embarrassment of the local blood supply. Bed rest is important in order to prevent spread of the inflammatory process. Smears of the secretions should be obtained from the lesion, and cultures grown therefrom, to determine the types of bacteria, and, through sensitivity tests, the proper antibacterial agents to be used These should be applied locally and also administered parenterally

Use of Vasodilating Agents. Attempts should be made to improve the cutaneous circulation through the use of drugs and procedures which either temporarily or permanently remove vasomotor tonus or augment the blood supply of the skin through some other means. Of value in this regard are the various adrenergic blocking agents, such as *Priscoline, Dibenzyline, Hydergine*, and *nicotinic acid* The application of heat to distant portions of the body, to produce reflex or indirect vasodilatation of the blood vessels in the involved extremity, is a worth-while procedure, as is the oral use of whiskey The various mechanical procedures, such as *postural exercises* (Buerger's exercises), *Sanders' oscillating bed, pavaex boot*, and *intermittent venous occlusion*, are of little use in the treatment of an ulcer or gangrene.

Sympathectomy is of value in delineating the lesion, and, if gangrenous digits are to be removed, in facilitating healing of the stumps. However, if extension of the process onto the adjoining portion of the foot or hand has occurred, the operation is not indicated Whether or not it permits a lower level of amputation of an extremity cannot be determined on the basis of available evidence

GENERAL DIRECTIONS FOR CARE OF THE FEET

1. Wash feet each night with a facial soap and warm water.

2. Dry feet with a clean soft rag *without* rubbing the skin. Dry carefully between the toes.

3. Always keep your feet warm Wear woolen socks or wool-lined shoes in the winter and white cotton socks in warm weather. Use a clean pair of socks each day.

4. Wear loosely fitting bed socks.

5. Never apply a hot-water bottle, an electric pad, or any other form of mechanical heating device to your extremities.

6. Wear properly fitting shoes and be particularly careful that they are not too tight Use shoes made of soft leather.

7. Cut your toenails in a very good light and only after your feet have been soaked in warm water and cleansed thoroughly. Cut the toenails straight across Do not cut down into the corners of the nails. If your feet are cared for by a chiropodist, be sure to tell him about your difficulties.

8. Do not cut your corns or callouses. Never use corn plasters or corn medicine. Instead take the pressure of your shoes off corns, bunions, or callouses, by using pads or wearing larger shoes

9. Do not use circular garters.

10 Do not use strong antiseptic drugs on your feet, particularly tincture of iodine, Lysol, or carbolic acid.

11. Seek medical care at the first signs of a blister, infection of the toes, ingrowing toenails, or trouble with bunions, corns, or callouses.

12. Have some member of your family examine your feet at least once a week for blisters, sores, or other wounds.

13 Avoid getting athlete's foot. If it occurs, be very careful how you treat it. Seek your doctor's advice on the matter.

ARTERIOSCLEROSIS OBLITERANS

With the progressive extension of life expectancy, especially in the case of diabetic patients, an increase in the incidence of arteriosclerosis obliterans can be anticipated. Even at present, this disease is by far the most common of the occlusive arterial disorders

Pathogenesis. Although a number of views have been expressed regarding the causative agent in arteriosclerosis obliterans, none has been universally adopted. The opinion that has recently been exposed to experimental study suggests that an abnormal metabolism of fat and other lipids is responsible for the formation of atheromatous plaques (Gofman et al 1950a). Abnormal vascularization of the arterial wall has also been suggested as a possible factor in the production of these lesions (Leary, 1938, Wartman). Another view is that atherosclerosis results from the prolonged stress and strain to which arteries are subjected during the life of the individual, i.e.,

that it is a reflection of the natural aging process

Clinical Picture and Course. SYMPTOMS Not infrequently arteriosclerosis obliterans may exist for a long time before symptoms appear. This is due to the fact that the occlusive process generally progresses at such a slow pace that sufficient time exists for the formation of an adequate collateral circulation. Only when there is an acceleration of the rate of occlusion of main vessels or a reduction in the efficiency of the secondary circulation will the patient begin to experience the pain in the extremities which is typical of intermittent claudication Rest pain is also a common complaint; this is due to a reduced blood supply to the peripheral nerves With the onset of ulceration or gangrene, almost continuous pain may be experienced in the vicinity of the lesion

SIGNS. The objective findings in arteriosclerosis obliterans are similar in all regards to those observed in thromboangiitis obliterans, namely, *absent or reduced pulsations in the main vessels of the foot and leg*, absent or reduced oscillometric readings at the various levels on the leg and thigh, and abnormal color changes in the horizontal, elevated, and *dependent* positions Generally the feet are *dry* and *cold* rather than wet and cold, as they are in thromboangiitis obliterans.

Spontaneous trophic changes usually occur in the most distal portions of the limb, the toes and the heel (Fig. 15-19), although trauma to any part of the limb may precipitate the formation of an ulcer. In diabetic patients, secondary infection frequently plays a role in the further progression of the ulcerative or gangrenous process (Fig 15-19B).

Differential Diagnosis. The main difficulty encountered in the differential diagnosis of arteriosclerosis obliterans is its similarity to thromboangiitis obliterans. However, there are certain points which are helpful in making the differentiation, among them is the age of the patient at the time of onset of the condition. Arteriosclerosis obliterans usually begins in persons between the ages of 45 and 70 years, in diabetics, however, it may occur prematurely. In contrast, thromboangiitis obliterans



Fig. 15-19 *Trophic changes in arteriosclerosis obliterans* A. Involvement of great toe and adjoining portion of foot, ultimately *requiring* a supracondylar amputation B Gangrene and infection in a patient with associated diabetes mellitus C Rapidly spreading gangrene

has its inception in relatively younger individuals, 16 to 40 years of age. This disorder is invariably present in people who smoke, a relationship which is not necessarily noted in arteriosclerosis obliterans Furthermore, as has been mentioned, a history of superficial migratory thrombophlebitis can be elicited in somewhat less than half the cases of Buerger's disease, in contrast, arteriosclerosis obliterans is never associated with pathological changes of the veins

Calcification of the blood vessels (Monckeberg sclerosis), as determined by soft-tissue x-ray technique, is not noted in thromboangiitis obliterans, while it may be present in arteriosclerosis obliterans. Furthermore, in the latter condition, there may be signs of generalized arteriosclerosis, such as coronary insufficiency, arteriosclerotic changes in the retinal vessels, and nephrosclerosis. Such abnormalities do not exist in uncomplicated cases of thromboangiitis obliterans Finally, the pathological process in thromboangiitis obliterans may affect the arteries in the upper extremities (Fig. 15-18) much more often than is the case in arteriosclerosis obliterans.

Arteriography has also been utilized in differentiating between the two conditions. In arteriosclerosis obliterans, the arteries demonstrate irregular and eccentric filling defects and segments of complete occlusion (Fig. 15-20). Visualization of the vessels below the block is frequently observed, as a result of the movement of contrast material through the diffuse network of collateral channels generally found bridging the obstructed portion of artery. In contrast, in thromboangiitis obliterans, the vessels show narrowing but not the filling defects,



Fig. 15-20. Arteriography in arteriosclerosis obliterans. A Segmental thrombosis of femoral artery, showing bridging collateral channels and filling distally. Deep femoral artery is patent. B. Block of the femoral artery close to the origin of the deep femoral artery Numerous collateral vessels are noted.

although sites of complete occlusion may be present For the most part, the vessels are less tortuous than they are in arteriosclerosis obliterans.

Among the findings which are common to the two conditions is the symptom of *intermittent claudication* This complaint, which may manifest itself in the form of a sense of tiredness or fatigue, a dull ache, a sensation of tightness or compression, a cramp or a sharp pain, is always elicited by physical effort and is located in the exercising muscles Its presence indicates that there is an insufficient blood supply to take care of the markedly increased metabolic requirements of the tissues during physical stress. With cessation of effort, this situation no longer exists, with the result that now the impaired local vascular system is again adequate Consequently the pain subsides Obviously there should be no difference in the symptoms experienced on walking in either arteriosclerosis obliterans or thromboangiitis obliterans, since in both there is a reduction in the efficiency of the muscle circulation during exercise.

Rest pain is also common to the two conditions, in each case indicating the presence of an ischemic neuritis due to an impaired circulation to the peripheral nerves. Finally, the nutritional disturbances are similar in appearance, since they have a common causative agent, namely, a decrease in cutaneous blood flow.

Complications. In contrast with thromboangiitis obliterans, arteriosclerosis obliterans may be associated with several serious complications Among them are spontaneous *arterial aneurysm* and complete *arterial thrombosis* The latter is usually superimposed upon a gradual occlusion of an artery and may have little deleterious effect, provided the previous prolonged state of chronic hypoxia has acted as an effective stimulus for the production of an adequate collateral circulation. In the absence of such a response, complete occlusion of a critical artery may be followed by the appearance of nutritional changes (Fig. 15-21B).



Fig. 15-21. A Gangrene of foot and adjoin... aneurysm of ... arte... men... Hoeber, 1956) ...son Diagnosis and Treat-

The formation of an arterial aneurysm in arteriosclerosis obliterans occurs as a result of the weakening of the medial coats of the affected segment of vessel This type of lesion is observed more frequently in the popliteal artery than in any other vessel in the limb while involvement of the femoral artery is next in frequency. The condition is diagnosed on the basis of the presence of a *pulsating mass;* a thrill and bruit over the lesion are rather inconstant findings. A serious consequence of an arterial aneurysm is the liberation of small emboli from the clotted material, which may enter the blood stream and occlude distal vessels. Another complication is spontaneous acute thrombosis of the lesion, causing occlusion of the portion of the artery from which it arises (Fig. 15-21A). Rupture and hemorrhage of the aneurysm may place the patient's life in jeopardy

Prognosis. The prognosis in arteriosclerosis obliterans depends in great part upon the degree of simultaneous involvement of vital organs elsewhere in the body, rather than upon the changes in the extremities alone. Since the pathologic process in the blood vessels of the limbs is progressive, the appearance of nutritional disturbances depends upon the efficiency of the collateral circulation. If the latter continues to grow at a rate which is sufficient to offset the slow occlusion taking place in a main arterial trunk, then ulcers or gangrene will not occur Of course, if the existing equilibrium is destroyed, as by trauma to the extremity, then they may appear. The presence of diabetes may contribute to the gravity of the situation because of its deleterious effect upon the resistance of tissues to infection

Treatment. The regimen outlined above for the local treatment of the extremities of patients with thromboangiitis obliterans applies equally well to individuals with arteriosclerosis obliterans. This is also true for the sections on physical activity and treatment of ulcerative or gangrenous lesions.

With regard to *tobacco smoking*, the evidence that this habit has a detrimental effect upon patients with arteriosclerosis obliterans and causes progression of the occlusive process is not as clear-cut as in the case of thromboangiitis obliterans. Nevertheless, it is still advisable for a patient with arteriosclerosis obliterans to abstain from it, on the basis that smoking is a potent vasoconstricting stimulus which affects the cutaneous circulation, thus decreasing the nourishment to the skin

ARTERIAL EMBOLISM

Sudden embolic occlusion of a critical artery in the extremities is a real emergency, and therefore its early clinical recognition is essential in order to institute proper therapy immediately.

Origin. Arterial *emboli* may arise in a number of sites, the most common being a fibrillating left atrium. Even in the absence of atrial fibrillation, thrombi may form in this chamber if it has become dilated as the result of some disease. The next most common site is a mural thrombus in the left ventricle, following a myocardial infarction (Fig 15-22A). Other, less frequent, sources include a mural thrombus superimposed upon an arteriosclerotic plaque in the abdominal aorta, an aneurysm of the aorta or a main branch thereof, or valve cusps made friable by bacterial endocarditis Emboli generally lodge at the point of bifurcation of a vessel (Fig 15-22B) or where its lumen suddenly narrows.

Pathogenesis. When an artery is suddenly occluded by an embolus, blood flow distal to the occlusion ceases. At the same time the involved vessel segment acts as an irritable focus to initiate vasospasm of the unaffected collateral channels in the limb, thus further aggravating the state of hypoxia of the tissues As a result, viability may be lost and nutritional disturbances may appear.

Clinical Picture. SYMPTOMS. The initial complaint following occlusion of an artery is pain in the distal portion of the limb. This may be sharp or dull, but is usually quite severe. Various symptoms indicating ischemia of nerve structures may be experienced, such as *paresthesias* in the digits, a sensation of *numbness* or "walking on a block of wood," and inability to perform voluntary movements of the digits Associated with these complaints may be symptoms at the level of the occlusion, which are usually of short duration.

SIGNS The findings associated with sudden occlusion of a critical artery are frequently quite typical and are the result of the markedly impaired arterial circulation. The distal tissues are either *pale* in color, because of absence of blood in the subpapillary venous

plexus, or *mottled*, due to trapping of blood in some of the cutaneous venules or veins. Skin temperature is low and the superficial veins are *collapsed*. A neurologic examination generally reveals a stocking-glove type of anesthesia or hypesthesia, with *inability to move the digits.* Pulsations and oscillometric readings are absent below the occlusion and somewhat reduced or at times increased above this site.

Course and Complications. Following arterial embolism, either the circulation through the collateral vessels gradually improves, permitting the distal tissues to remain viable, or the prolonged period of hypoxia results in the appearance of *gangrene* (Fig. 15-23). The latter development is generally followed by amputation of the limb, unless the process is limited to a digit or digits and does not affect the adjoining *portion of the extremity. If irreversible* signs of destruction of tissue do not appear in the first 3 or 4 days after the onset of the condition, there is a good possibility that the viability of the limb will be maintained. However, if no attempt is made to prevent propagation of the clot, progressive occlusion of collateral vessels may cause the appearance of *nu-*





Fig. 15-22. A Mural thrombus in left ventricle, following a myocardial infarction, responsible for embolic phenomena in the left lower extremity. B Embolus at the bifurcation of the left common iliac artery, with propagation into the external and internal iliac arteries. (From Abramson, Diagnosis and Treatment of Peripheral Vascular Disorders. Hoeber, 1956.)

tritional disturbances later in the course of the disease.

Diagnosis. The diagnosis of an arterial embolism must be seriously considered whenever a marked impairment of arterial circulation to a limb appears suddenly in a patient who has previously had a normal vascular tree but is a potential candidate for thrombus formation. To initiate proper treatment, it is necessary not only to recognize the disorder in its early stages, but also to determine the exact location of the embolus. For this purpose, oscillometric studies and palpation of pulsations are essential; the examiner must keep in mind the usual locations for lodgment of the clots. At times the superimposed vasospasm may lead to erroneous conclusions and, when this possibility exists, vasomotor tonus should be removed by the use of paravertebral sympathetic, epidural, or spinal block, and the clinical findings then reevaluated.

The one entity which is difficult to differentiate from arterial embolism is arterial thrombosis and, in some instances, differentiation is impossible. Important data are a history of intermittent claudication and the previous existence of signs of impaired arterial circulation in the limb, as well as the absence of a possible site for the origin of emboli, in the case of arterial thrombosis.

Prognosis. Once the acute phase has subsided and death of tissue has not occurred, the immediate prognosis for the viability of the limb is good. Generally the collateral circulation becomes more efficient with time and the nutritional state of the skin approaches normal However, if the muscles have been left with an impaired arterial circulation, the patient may suffer from intermittent claudication

The long-range prognosis in arterial embolism depends on whether or not the cause for the original episode still operates. If it does, the possibility of recurrence of this condition in other parts of the body, including the brain, should be kept in mind. The outlook will then depend upon which vessels are occluded.

Treatment. Once the diagnosis of arterial embolism is made, a rapid-acting anticoagulant like *heparin* should immediately be given intravenously to prevent propagation of the thrombotic process distally and into the collateral vessels. The next step is to prepare the patient for an *embolectomy*, provided a critical artery is occluded and the site of embolism can be accurately determined. Lodgment of an embolus in the aortic bifurcation, the common and external iliac arteries, and the femoral and the popliteal arteries in most instances necessitates immediate embolectomy. On the other hand, there appears to be no need to remove emboli from the radial, ulnar, posterior tibial, and dorsalis pedis arteries, and this procedure is rarely carried out in the case of the brachial artery above its bifurcation.

Following embolectomy, *anticoagulant therapy* should be continued, substituting a slow-acting drug like *Dicumarol* for heparin The limb should be covered with cotton dressings to preserve its own heat, but neither heat nor cold should be applied locally. Furthermore, the limb should be left in the horizontal position and not elevated or placed in dependency. This type of regimen is also used in the case of the patient not subjected to embolectomy.

With regard to the proper approach for preventing further embolic episodes, no unanimity exists. It has been suggested that the patient remain on anticoagulant therapy for the rest

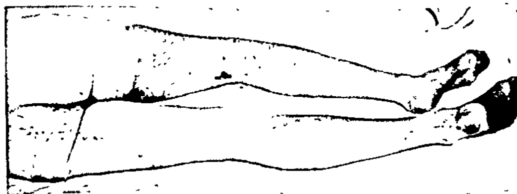


Fig. 15-23. Saddle embolus at bifurcation of aorta, causing gangrene of both lower extremities. (From Abramson. *Diagnosis and Treatment of Peripheral Vascular Disorders.* Hoeber, 1956.)

of his life. However, it is realized that in many instances such a course is impracticable. Furthermore, it is usually difficult to maintain continuously the necessary reduction in prothrombin activity through the unsatisfactory type of medical supervision available with home therapy. In the case of mitral stenosis, mitral commissurotomy and atrial appendectomy have been utilized to reduce the possibility of thrombus formation in the left atrium, but the number of cases studied up to the present has been insufficient to determine whether or not such a procedure has merit.

POLYARTERITIS (PANARTERITIS, PERIARTERITIS) NODOSA

Polyarteritis nodosa is a generalized vascular disease, principally affecting medium-sized arteries It is considered to fall within the category of "collagen vascular disorders."

Causative Factors. The cause of polyarteritis nodosa has not been determined, although several possibilities have been suggested, among them the factor of hypersensitivity. In favor of this view are certain experimental studies in which lesions typical of polyarteritis nodosa were produced by the injection of various antigens into sensitive animals (Rich and Gregory). Further evidence consists of the correlation that has been noted between polyarteritis nodosa and allergic phenomena of various types. However, the possibility has not been excluded that a hypersensitivity angiitis exists, which is similar to but not identical with polyarteritis nodosa (Churg and Strauss). Psychogenic influences acting through the adrenal cortex have also been proposed as a possible etiologic agent.

Clinical Picture. SYSTEMIC RESPONSE Since polyarteritis nodosa is a widespread disease, the symptoms are generally quite diverse. A low-grade, irregular and recurrent *fever* is frequently noted at some time in the course of the disease This is usually associated with such systemic responses as chills, malaise, prostration, and changes in the peripheral blood indicating the presence of some type of inflammatory process.

CHANGES IN THE LIMBS In the extremities, polyarteritis nodosa may be manifested by involvement of several different types of tissues. There may be ischemic ulcerations, due to thrombosis of cutaneous arterioles, or aneurysmal dilatations of the main arteries, taking the form of *subcutaneous nodules* along the course of the vessels. Nonspecific skin lesions may also be present. The peripheral nerves may be affected, producing symptoms and signs resembling a polyneuritis. These consist of numbness and tingling, paresis of the extensor muscles of the wrist, and wrist drop, similar types of change in the lower extremities, and some impairment of the perception of vibration and the sense of touch. Finally, there may be changes in the musculoskeletal system, in the form of fibrillation and atrophy of voluntary muscles, associated with pain, tenderness, and weakness.

INVOLVEMENT OF OTHER PORTIONS OF THE BODY. Most of the vital organs may be affected by the disease process. Pathologic changes in the *vessels of the brain* may produce atypical hemiplegia and cerebellar symptoms and signs. Convulsions and findings suggesting meningeal irritation may also be present. When the *kidneys* are affected, hypertension generally follows In some instances, renal insufficiency and even uremia may occur. With involvement of the *heart*, dyspnea, palpitation, and precordial pain may appear. Pathological changes in the *gastrointestinal tract* are manifested in the form of anorexia, vomiting, and weight loss, and the more serious complication of mesenteric artery thrombosis. The presence of a cough, pain in the chest, and asthmatic attacks may indicate alterations in the *pulmonary arteries*. Other findings indicative of lung involvement are pleuritis, bronchiectasis, and atelectasis.

Laboratory Data. A common finding in polyarteritis nodosa is the presence in the urine of albumin, blood, and various types of casts (red-blood-cell casts, oval fat bodies, fatty and waxy casts, and broad casts). Also of diagnostic importance are the changes in the peripheral blood. These consist of a *leucocytosis*, sometimes to as high as 50,000/mm³, and an *eosinophilia*. However, the absence of the latter does not rule out the possibility of polyarteritis nodosa Actually, it is necessary to examine numerous blood samples before concluding that this type of abnormality is not present. If the eosinophilia continues to increase, it can be interpreted as indicating activity of the disease. A secondary anemia and an elevated sedimentation rate may be associated with the changes in the white blood cells

tritional disturbances later in the course of the disease.

Diagnosis. The diagnosis of an arterial embolism must be seriously considered whenever a marked impairment of arterial circulation to a limb appears suddenly in a patient who has previously had a normal vascular tree but is a potential candidate for thrombus formation. To initiate proper treatment, it is necessary not only to recognize the disorder in its early stages, but also to determine the exact location of the embolus. For this purpose, oscillometric studies and palpation of pulsations are essential; the examiner must keep in mind the usual locations for lodgment of the clots. At times the superimposed vasospasm may lead to erroneous conclusions and, when this possibility exists, vasomotor tonus should be removed by the use of paravertebral sympathetic, epidural, or spinal block, and the clinical findings then reevaluated.

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With regard to the proper approach for preventing further embolic episodes, no unanimity exists. It has been suggested that the patient remain on anticoagulant therapy for the rest

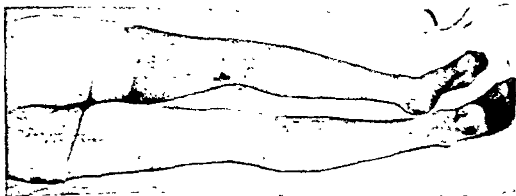


Fig. 15-23. Saddle embolus at bifurcation of aorta, causing gangrene of both lower extremities. (From Abramson, *Diagnosis and Treatment of Peripheral Vascular Disorders*. Hoeber, 1956.)

mild emotional strain. In many instances, however, the severity of the condition remains unchanged.

The sequence typical of the color changes is pallor during the period in which the exciting stimulus operates, cyanosis, rubor, and then a return to the normal color. However, it is not necessary to observe all of the abnormalities in order to make the diagnosis. For example, cyanosis may be the initiating color, while pallor may be absent, or pallor may be followed by rubor without the appearance of cyanosis. In some instances, pallor or cyanosis may be replaced by a normal color without rubor intervening. To be able to make the diagnosis, either pallor or cyanosis should be noted initially.

It is necessary to emphasize that the color change in Raynaud's disease is limited to the digits and that it does not extend on to the adjoining part of the hand or foot. It generally is noticed first in the tips and later in the more proximal portion of the phalanges. Early in the disease, there may be a unilateral color change, but eventually bilateral distribution, with symmetrical digital involvement, is noted. At no time is there a reduction in or absence of pulsations in the main artery to the limb, and the results of various tests for arterial efficiency are generally normal.

Mild trophic changes may appear in the involved digits, such as abnormal growth or brittleness of the nails, loss of subcutaneous tissue, and calcium deposits in the finger tips. At times, there may be more severe abnormalities such as atrophic arthritis and sclerodermatous alterations in the skin (*sclerodactylia*). Superficial ulceration and gangrene of the tips of the digits may also occur (Fig 15-24). The excruciating burning sensation frequently associated with these lesions is usually much out of proportion to their apparent severity.

PROGNOSIS. It is important to reassure the patient with Raynaud's disease that, although the condition may cause great inconvenience at times and may even interfere with his daily activity, it is still a relatively benign disorder. The fact that the attacks can be controlled to some extent by eliminating the agents which initiate them is in contrast with the more serious occlusive arterial vascular disorders, in which progression of the pathological state frequently occurs regardless of what approach is utilized as treatment. In those instances of Raynaud's disease in which superficial ulceration or gangrene is noted, the lesions are usually limited to the distal portion of the digits and rarely require amputation of a finger.

TREATMENT *Protection from Noxious Stimuli or Trauma.* One of the most important steps in the treatment of Raynaud's disease is the reduction or elimination of those conditions which initiate the digital spasm. Because cold is very potent in this regard, it is necessary to decrease the periods of exposure of the body, and particularly the extremities, to this agent to a minimum. The hand warmer used by sportsmen is of value in preventing attacks while the patient is outdoors. Mittens should be worn in preference to gloves since they produce less constricting effect on the digits.

Because of the proved vasoconstricting ef- [illegible] tween smoking and the progression of this disorder, although it has been noted in the case

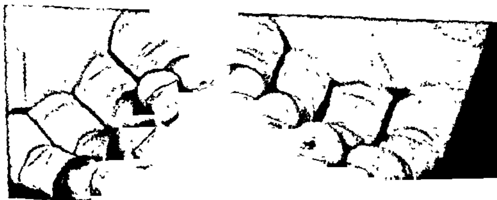


Fig 15-24 Small ulceration of finger tips in Raynaud's disease

Since polyarteritis nodosa may mimic a great number of systemic disorders, it may be necessary in many instances to resort to a *biopsy* study of a subcutaneous nodule or a section of skeletal muscle before arriving at the proper diagnosis. In order to obtain definitive information by such a means, however, the specimen of muscle should be removed from a site in which pain and tenderness are experienced.

Prognosis. The outlook in polyarteritis nodosa is grave, with the usual acute case going on to total debility and death in a period of from several weeks to several months. Nevertheless, it is necessary to point out that there may be exacerbations and remissions, with healing occurring in some instances. It is also possible that there are mild cases in which the diagnosis is infrequently made. Death in polyarteritis nodosa generally results from congestive heart failure or renal insufficiency and, less frequently, from hemorrhage due either to the rupture of an aneurysm or to necrosis of critical organs.

Treatment. Therapy in polyarteritis nodosa has, for the most part, been symptomatic and supportive, involving the administration of proper diet, the use of antibiotics for intercurrent infections, the control of congestive heart failure, and the treatment of painful muscles and joints with orthopedic appliances. Recently, however, *cortisone* and *corticotropin (ACTH)* have been utilized, with prompt relief of symptoms and disappearance of fever in many instances. However, relapses have generally occurred with termination of the medication. At present, it is still too early to give the final evaluation of this type of therapy, although it appears to hold promise

SPECIAL VASCULAR SYNDROMES

Raynaud's Disease. Raynaud's disease is a functional or vasospastic vascular disorder, which is typified by episodes of color changes in the fingers and toes, initiated by exposure to cold or by emotional excitation In order to make this diagnosis, it is necessary to demonstrate that no apparent causative factor exists. If one does, then the condition is considered to fall within the category of *Raynaud's syndrome* or *phenomenon* To support the diagnosis of Raynaud's disease, the episodes of color changes should be present for at least 2 years without the appearance of any of the signs or symptoms of an occlusive arterial vascular disorder.

PATHOGENESIS. Typically, the initial color change is *pallor* of the digits, produced by spasm of the digital arteries This may be followed by *cyanosis,* which is probably due either to a slow flow of blood through the capillaries, as a result of intermittent removal of spasm from the digital arteries, or to simultaneous spasm of digital veins, interfering with the movement of blood out of the tissues. As a consequence, there is a greater opportunity for the removal of oxygen from the blood as it passes through the capillary bed, so that the quantity of reduced hemoglobin in the subpapillary venous plexuses is increased, resulting in cyanosis of the skin. *Rubor,* which is generally the final color change, occurs after spasm of the digital arteries abates. It is a manifestation of the stage of reactive hyperemia which follows a period of lack of circulation to tissues.

The cause for the initiation of spasm of the digital arteries is not clear. It has been suggested (Heinbecker and Bishop; Hyndman and Wolkin) that the vessels themselves have an inherent increased sensitivity to cold, or that there is an abnormality in the innervation of the sympathetic nervous system (Adson; Simpson et al).

Since Raynaud's disease is a functional vascular disorder, it is generally not associated with permanent alterations in the digital arteries However, if the condition has existed for a long time or if various types of nutritional disturbances are present, histologic examination may reveal intimal hyperplasia and other pathologic changes in the terminal branches (Lewis, 1938).

CLINICAL PICTURE. Raynaud's disease is seen predominantly in young women, although it does occur on occasion in young men (Hines and Christensen, Abramson and Shumacker). Generally associated with the episode of pallor or cyanosis is a sense of coldness, numbness, or tightness in the involved digits. As the digital spasm wears off and the circulation is reestablished, paresthesias or burning or throbbing sensations may be experienced in the fingers. With progression of the condition, the attacks of color change may become more frequent and be elicited by even a slight reduction in the temperature of the environment or by

tree and characterized by periods of very severe burning sensations in the extremities and increased cutaneous temperature and rubor of the involved portions The attack is generally initiated by a rise in the environmental or body temperature. Although there are some workers (Lewis, 1933) who believe that this condition is a symptom complex, existing in many disorders, there appears to be sufficient evidence to warrant utilizing the term "primary erythromelalgia" for certain cases to denote a definite clinical entity

PATHOGENESIS The typical findings are probably related to the associated increase in local circulation invariably noted during an attack. However, there are probably other factors contributing to the pathogenesis of the condition, since an increase in peripheral blood flow in a normal limb, equal to that observed in erythromelalgia, does not ordinarily induce a burning sensation.

CLINICAL PICTURE AND DIAGNOSIS An important clue in the diagnosis of erythromelalgia is a history detailing the onset of the characteristic signs and symptoms after the extremity has been subjected to a high environmental temperature or to exercise. It is of interest that a definite elevation of temperature is necessary to precipitate the attacks and that below this point they are absent. In determining whether erythromelalgia exists, it may be necessary to attempt to initiate the burning sensation by raising the environmental temperature beyond the critical level

In "primary erythromelalgia" all the results of tests for circulatory efficiency are normal During an attack, the amplitude of the peripheral pulses and the oscillometric readings may be greater than normal In the differential diagnosis of the disorder, other conditions which could conceivably be responsible for the typical severe burning sensation in the extremities must be excluded Among them are polycythemia vera, thromboangiitis obliterans, peripheral neuritis associated with diabetes, pernicious anemia, and pantothenic acid deficiency.

PROGNOSIS Although primary erythromelalgia may produce considerable discomfort and even disability if the attacks are frequent, it is never associated with any untoward effects of a serious nature

TREATMENT No specific therapy exists for primary erythromelalgia. The important approach is the elimination of the initiating agent, i e, a rise in cutaneous temperature. The feet should be exposed to a cool environment as much as possible. If the attacks are causing enough difficulty to interfere with daily activities, it may be necessary to advise the patient to move to a more moderate climate.

A treatment of value consists of an attempt to decrease the sensitivity of the cutaneous vessels to heat by placing the involved extremities in water at a temperature low enough to produce no complaints and then gradually increasing the water temperature until discomfort is elicited. By means of repeated immersions, it may be possible to accustom the limbs to the critical temperature or even levels beyond this point. As temporary measures, certain medications are valuable in reducing the severity of the symptoms. Among these are *aspirin*, *ergotamine tartrate* in combination with *belladonna*, intravenously administered *calcium gluconate*, and 1:1,000 solution of *epinephrine* administered by inhalation (Mufson). The severity of the attack can be diminished somewhat by wrapping the affected extremities in cold, wet cloths or immersing them in ice water.

Immersion Foot and Trench Foot. CAUSATIVE FACTORS. Both trench foot and immersion foot result from exposure of the lower extremities to a cold, wet environment for a relatively prolonged period of time. The degree of cold necessary to produce these conditions is generally close to 32°F. The associated moisture augments the detrimental effect of the cold, since water has a high capacity for absorbing heat and thus causes better transmission of the cold to the tissues.

Trench foot occurs in combat and results from wearing wet socks and other wet footgear for days on end. Immersion foot is the seagoing counterpart, and is found in survivors of shipwrecks who have been compelled to sit for many hours, immobile, in a crowded, open lifeboat or raft with their feet immersed in water

PATHOGENESIS The basis for the pathologic changes observed in trench foot and immersion foot is probably *vasoconstriction*, followed by prolonged *hypoxia*, resulting from exposure of the tissues to cold As a consequence, there is sufficient damage to the capillary wall to permit movement of fluid into the tissue spaces, with

of thromboangiitis obliterans. If the patient cannot abstain, at least he should make every attempt not to smoke when outdoors in the cold.

Since minor bruises or even a pinprick may be sufficient to initiate superficial ulceration, the patient must be warned to protect his digits from injury. At times it may be necessary to advise a change in the type of daily activity if the work carries with it the possibility of trauma to the extremities.

Removal of Vasomotor Tonus. Another worth-while therapeutic approach is the utilization of procedures or medications which temporarily or permanently eliminate sympathetic control over the digital arteries. Among them are the sympathetic blocking agents such as *Priscoline*, *Hydergine*, and *Dibenzyline*. These drugs cause temporary inhibition of vasomotor tonus and thus lead to a reduction in the reactivity of the peripheral vessels to cold. Whiskey and other alcoholic beverages may also have a beneficial action, particularly during an episode of digital spasm.

It is generally agreed that *sympathectomy* produces beneficial effects in Raynaud's disease through a reduction in the intensity of the vasoconstricting response to local cold and through elimination of reflex vasoconstriction initiated by distant stimuli. However, in the case of the patient with Raynaud's disease who is not suffering from nutritional disturbances, this procedure should be resorted to only when the attacks of digital color change are numerous and disabling and are limited to one or two extremities. When three or four limbs are involved, the operation is not indicated, since the resulting widespread sympathetic denervation might cause marked impairment in the efficiency of the mechanism of heat loss from the body through sweating.

In the presence of infected ulcerations or superficial gangrene of the finger tips, sympathectomy has a definite place in therapy. It will frequently cause rapid improvement in the condition even after prolonged conservative therapy has been ineffectual. However, it is necessary to point out that, once healing has occurred, recurrences of nutritional disturbances in other digits may still take place

Psychotherapy. Since emotional excitation may be a potent stimulus for the production of digital spasm, every patient with Raynaud's disease should receive a certain amount of guidance in making a mental and physical adjustment to his disability. The individual who is markedly responsive to this type of stimulus and who, as a result, suffers from nutritional disturbances, may find it necessary to seek psychiatric care.

Acrocyanosis. Acrocyanosis is another functional or vasospastic condition, characterized by a persistent, uniform, cyanotic rubor of the skin of the hands, forearms, feet, and legs. The color change is present in a warm as well as a cold environment, although it is more marked in the latter.

PATHOGENESIS. Although the underlying mechanism is not clear, it has been suggested that the cause for the color change is prolonged *arteriolar spasm*, associated with capillary and venous paralysis. The available evidence does not implicate the sympathetic nervous system Because of the resulting slowed flow through the capillary bed, a greater opportunity is afforded for the removal of oxygen by the tissues As a consequence, the blood entering the subpapillary venous plexuses contains a larger than normal quantity of reduced hemoglobin, which is responsible for the cyanotic color of the skin.

CLINICAL PICTURE. The typical alteration observed in acrocyanosis is a deep-purple color of the skin on exposure to extreme cold and a red appearance in a warm environment. The change is persistent, except for its intensity, and does not occur in the form of episodes as noted in Raynaud's disease. Furthermore, the abnormal color is not limited to the digits, but involves the entire hand or foot, as well as the adjoining portion of the limb. As in the case of Raynaud's disease, all tests of arterial circulation indicate no involvement of the main arteries.

PROGNOSIS. Acrocyanosis is associated with no sequelae of serious consequences. It, therefore, can be considered to be a relatively benign functional disorder. However, it may cause a certain amount of discomfort and disability for some individuals.

TREATMENT. The only therapy for acrocyanosis is avoidance of exposure to cold. The use of sympathetic blocking agents has been proposed but appears to have little value.

Erythromelalgia. Erythromelalgia is a functional vascular disorder affecting the arterial

tree and characterized by periods of very severe burning sensations in the extremities and increased cutaneous temperature and rubor of the involved portions. The attack is generally initiated by a rise in the environmental or body temperature Although there are some workers (Lewis, 1933) who believe that this condition is a symptom complex, existing in many disorders, there appears to be sufficient evidence to warrant utilizing the term "primary erythromelalgia" for certain cases to denote a definite clinical entity.

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Fig. 15-25. Gangrene of feet in trench foot.

the development of *edema*. At the same time hemoconcentration and sludging of the blood occur; both of these are conducive to local thrombosis.

Another mechanism which contributes to the death of tissues is the initial hyperemic stage, during which the metabolic needs are raised, but an adequate local blood supply to satisfy them is not available. The changes observed during this period may be due either to an inflammatory reaction to cold, to vasomotor paralysis following interruption of vasoconstrictor fibers in the peripheral mixed nerves, or to direct damage to the vessel wall.

CLINICAL PICTURE Trench foot and immersion foot may be divided into several clinical stages. In the first, or prehyperemic stage, the symptoms may be of a minor degree, consisting of numbness, aching, and tingling. At this time the involved foot is initially red and later white. The arterial pulsations are reduced or absent because of the associated vasospasm

As recovery takes place, the hyperemic stage appears. Now the pulsations in the main arteries are bounding and the feet are red, hot, and dry. There may be petechial hemorrhages due to ruptured capillaries, and there may also be vesicles filled with straw-colored fluid. Superficial and deep gangrene may be noted (Fig 15-25).

In the last, or posthyperemic, stage the signs of vasodilatation gradually subside The swelling and blisters disappear, the skin temperature of the feet drops and marked sensitivity to cold is experienced. There may be hyperhidrosis, rigidity, pain in the ankles and other joints on walking, and weakness and deformities of the feet, in part due to disuse

PROGNOSIS. It is difficult to determine prognosis in trench foot and immersion foot since the question of government compensation will continue to plague the examiner and cast doubt on the authenticity of the reports obtained from the patients There is little question, however, that signs of excessive sympathetic tone will persist for many years. The patient will also continue to have a marked sensitivity to extremes of environmental temperature

TREATMENT. The question of treatment revolves around methods of preventing trench foot and immersion foot. Despite intense effort by the Army and Navy to reduce the incidence of these conditions, very little success has as yet been achieved. No shoe has been perfected which will satisfactorily prevent the feet from becoming cold and wet during combat

Initially, the active treatment should be directed at controlling the increase in metabolism that occurs during the hyperemic stage. Later, attempts should be made to counteract the atrophy of disuse and to make the patient assume a normal gait and again become ambulatory. Sympathectomy plays only a limited role in the treatment of the chronic stage of trench foot or immersion foot.

PRIMARY VARICOSITIES (VARICOSE VEINS)

Primary varicosities probably comprise one of the most common abnormalities in the category of peripheral vascular disorders, particularly among women. Because of the relative frequency of such complications as stasis dermatitis and ulceration, this condition is responsible for the loss of many productive hours from industry or household duties It therefore is of great importance to initiate appropriate treatment early in the disorder, before sequelae appear.

Causative Factors. Several factors have been proposed as possible causative agents in the production of *incompetent superficial veins* of the lower extremities One of these factors possibly is an inherent structural weakness of the valves in the affected vessels, a view which is supported by the frequent existence of a family history of varicosities Another is the hemodynamic effect of the erect position. Since there are no valves in the inferior vena cava and common iliac veins, the full hydrostatic action of the column of blood in the abdomen must normally be counteracted by the valves in the external iliac and femoral veins In the congenital absence of these structures in the latter vessels, an even greater burden of support is placed on the valve at the saphenofemoral junction It is this structure which is almost invariably affected when varicosities are present.

Other factors which may predispose to varicosities are heavy muscular work with straining at lifting, pelvic tumors, and mechanical constriction of the limb, such as produced by elastic supports, girdles, garters, and tight bandages. Obesity is an important factor, since subcutaneous fat supplies little effective support to the superficial veins. The fact that varicosities are predominantly present in females suggests that certain anatomic factors existing in this sex contribute to the production of venous stasis Among these are the broader pelvis and the increased hyperemia of the pelvic veins during puberty, menopause, menstruation, and pregnancy.

Pathogenesis. Varicosities are produced when the valves in the veins of the lower extremities become incompetent, thus allowing regurgitation of blood into the superficial venous system This may occur at the saphenofemoral junction or in the communicating or perforating vessels which join the superficial and deep venous systems at different levels in the thigh and leg Because the superficial vessels have poor support, they enlarge and become tortuous when the pressure within them rises abnormally As a consequence of the distention of the vessels, the valves become incompetent

Clinical Picture. SYMPTOMS The patient with varicosities may or may not have any symptoms Furthermore, there is not always a relationship between their severity and the degree and extent of involvement of the veins. The usual complaints consist of a *sense of heaviness* or *fullness* and *easy fatigue* in the involved limb, probably as a result of the venous stasis and increased weight of the extremity. The patient will note that the longer he stands in one position, the more marked will his symptoms become. On the other hand, elevation of the limb, and, to a lesser extent, walking, have a beneficial action. *Night cramps* are fairly common and appear to be dependent upon the amount of physical exertion undergone during the day.

SIGNS. Examination of the extremities invariably reveals the appearance of prominent, tortuous, superficial veins, which become more obvious when the patient stands (Fig 15-26). The presence of a regurgitant flow in these vessels is determined by the various tests described below.

Trendelenburg Test. This procedure, which is the one most frequently used, is of value in differentiating dilated from varicose superficial veins and also in determining whether or not incompetent communicating channels exist. The test is performed as follows:

With the patient lying on his back, the involved limb is elevated in order to empty the superficial veins and while the limb is in this position, a rubber tourniquet is applied around the thigh below the level of the fossa ovalis. The patient now stands, and within 10 sec the tourniquet is released An immediate filling *of the great saphenous vein from above downward indicates that the valve in this vessel is incompetent.* A normal response is a slow filling of the superficial veins (in about 30 sec or more) as a result of the movement of blood upward from the capillary system

The test can also be performed by maintaining the tourniquet in place with the patient in the upright position and determining the rate at which the veins fill below the level of the compression. The rapid appearance of dilated vessels when the patient stands indicates that there has been a reflux flow into them either from the small saphenous system or from incompetent communicating branches in the leg or lower thigh

Multiple Tourniquet Test This procedure, a modification of the Trendelenburg test, involves the use of four tourniquets, three applied to the thigh, so as to compress the upper, middle, and lower segments, respectively, and

one to the leg below the knee; the tourniquets are applied while the patient is lying down with his lower extremity elevated. He then assumes the upright position and the rate of venous filling below the level of the most distal tourniquet is noted. If the vessels below the knee become prominent rapidly, it can be assumed that there are incompetent communicating veins in the lower portion of the leg. If no change is noted, the most distal band is removed. Immediate filling of the superficial veins under these circumstances implies that the small saphenous vein is incompetent. In ascending order the three tourniquets on the thigh are then removed, the appearance of clusters of veins being sought after each step. If the change occurs following removal of the bands around the middle and the lower third of the thigh, it can be assumed that the venous channels in these sites, aside from the great saphenous vein, are incompetent. Sudden distention of the veins on the leg and thigh with release of the last tourniquet, on the upper third of the thigh, localizes the difficulty to the saphenofemoral junction

Percussion or Schwarz Test. This procedure is carried out by having the patient stand so as to fill the superficial veins, and then tapping the lower level of a distended vessel with a finger. The fingers of the other hand are at the same time placed over the upper segment of the vein. After determining whether or not an impulse is perceived by the examining fingers, the procedure is reversed, with the tapping being applied to the proximal portion of the vein near the fossa ovalis, and the palpating digits placed distally over the vessel Again, the desired information is whether or not an obvious impulse can be felt.

If incompetency exists, a disturbance will be initiated by the application of the blow which travels in either direction over the column of blood in the form of a wave In a vein with competent valves, proximal spread occurs to only a minor degree, while there is no distal spread



Fig. 15-26. A. and B. Primary varicosities of the greater saphenous system.

Venous Pressure Readings. The determination of the venous pressure in the foot has more experimental than clinical application, since it generally requires surgical exposure of a superficial vein on the dorsum of the foot and cannulation of a vessel by a No. 14 gage, thin-walled needle. Normally, the venous pressure reading in the foot varies with the position of the body. When the subject is lying down, it is the same as the pressure in the upper extremity (4 to 8 mm Hg). When the subject stands up, the pressure rises to a level equal to that in recumbency plus an increment representing the hydrostatic pressure of the column of blood between the heart and the point tested. The readings, therefore, vary between 70 and 100 mm Hg. When the subject is exercising, the pressure falls to 30 to 40 mm Hg, due to the pumping action of the muscles on the neighboring veins, which shunts the blood into the deep venous system and out of the limb.

In the presence of varicosities, the readings in recumbency are generally higher than those in normal individuals, while on standing they are approximately the same. With exercise, the drop ordinarily observed does not occur because blood is regurgitated from the deep venous system into the superficial veins. If a tourniquet has been previously applied to the thigh in order to prevent retrograde flow, walking will reduce the pressure to normal levels.

Complications. The complications of varicosities are generally due to the associated venous stasis, a chronic pooling of blood in the involved superficial veins, resulting in their overdistention. As a consequence, certain changes will take place in the skin: *edema*, first pitting and eventually nonpitting, *pigmentation*, stasis dermatitis, chronic indurated *cellulitis*, and finally *ulceration*. These changes are similar to those observed in the postphlebitic syndrome (Fig. 15-27). Ulceration has definite economic implications because if it has developed once it frequently recurs and thus renders the patient a semi-invalid, incapable of working for weeks and even months during each attack.

Prognosis. The outlook for the patient with varicosities depends to a great extent upon whether or not the above-mentioned complications can be prevented or, if they are present, whether they can be controlled and eliminated. It must be pointed out that, although temporarily disabling, they are never associated with immediate danger to life.

Treatment. MEDICAL. Medical treatment is of limited value in the control of primary varicosities, for the various procedures at best alleviate rather than cure the disorder. However, under certain circumstances, it is necessary to utilize one or several of them, either as a temporary measure or permanently, if there are contraindications to surgery. Conditions for which medical methods have been suggested are pregnancy, nonsymptomatic minor varicosities, and varicosities associated with local arterial impairment. With varicosities which have recurred after surgery and in treating certain psychoneurotic individuals, it is also probably better to use a medical approach. Finally, there is some question regarding the advisability of surgery for elderly and obese patients.

Elastic Support. The medical treatment of varicosities consists for the most part of the use of some type of elastic compression of the superficial veins. This can be accomplished through the application of elastic stockings or by means of elastic bandages.

Sclerosing Technique. The intravenous injection of a sclerosing agent has a limited use, except when it supplements surgical therapy. Only patients showing minor involvement are satisfactorily treated in this fashion. The procedure in no way reduces the reflux of blood occurring in the proximal portion of the extremity; as a result, while some vessels are obliterated by the sclerosing solution, others become varicose because of the shunting of blood into them. Another reason for the limited use of the injection technique is that recanalization of the thrombosed veins usually takes place because of the constant back pressure due to the retrograde flow of blood.

SURGICAL. The surgical approach is in most instances the proper treatment of varicosities. A number of methods have been utilized but as yet there is no unanimity as to which is the most effective. However, in recent years there has been a tendency to depend more and more upon high ligation of the great saphenous vein and extirpation of a part or all of this vessel by means of a stripper. Other methods which have been used are (1) high ligation of

the great saphenous vein at its junction with the femoral vein; (2) high ligation of the great saphenous vein, followed by retrograde injection of a sclerosing agent into the distal portion of the vessel; and (3) high ligation of the *great saphenous vein at its junction with the femoral vein*, plus multiple ligations and divisions of the vessel along its course.

SUPERFICIAL AND DEEP THROMBOPHLEBITIS

Inflammatory involvement (together with secondary thrombosis) of the walls of the veins in the extremities, is a relatively frequent occurrence, particularly in the case of the superficial venous system. Rarely is thrombosis present without the subsequent appearance of a phlebitic process The clinical picture will vary markedly depending upon whether the *superficial or deep set of veins is involved*

Etiology. A number of physiologic and pathologic states are conducive to the initiation of venous thrombosis Among these are venous stasis, direct trauma to the vessel wall, and alterations in the coagulability of the blood, caused by either injury to tissues elsewhere in the body or changes in the formed elements in the blood stream.



Fig. 15-27. Postphlebitic syndrome A. Chronic indurated cellulitis, with marked browniness and fibrotic reaction in skin. B. Stasis ulceration in usual site on medial aspect of ankle. C. Brown pigmentation and hyperkeratosis following prolonged venous stasis.

VENOUS STASIS This is one of the most important conditions contributing to intravascular clotting It may be initiated by physical inactivity, immobilization of the limb, the application of tight abdominal dressings, the assumption of Fowler's position, the use of pillows placed under the knees, and increased vasomotor tonus present during and immediately after an operative procedure. All of these factors interfere with venous return and cause pooling of blood in the veins of the lower extremities A similar situation may occur in severe congestive heart failure and during pregnancy.

INJURY TO THE INTIMA OF A VEIN. This type of change may result from crushing injuries to the limb, fractures, deep wounds, operative procedures in the pelvis, and the intravenous administration of irritating drugs. Trauma to veins may also occur following sudden and severe (or moderate but repeated) muscular contractions in the lower extremities Prolonged pressure of the weight of the leg on the calf muscles may likewise cause intimal damage. Malignant invasion of veins can produce the same type of change.

INCREASE IN THE COAGULABILITY OF THE BLOOD Such an abnormality may result from destruction of tissue elsewhere in the body, as in the case of a surgical procedure, extensive burns, a delivery, or infection The causative factors are probably a greater viscosity and an elevation of the fibrinogen content of the plasma In visceral carcinoma, which may be associated with venous thrombosis—particularly in the lower extremities—the cause is again most likely some type of change in the coagulation mechanism, possibly related to destruction of tissue by cancerous infiltration

Among the hematologic conditions characterized by a tendency toward blood coagulation is *polycythemia*, in which the responsible factor is the greater viscosity of the blood resulting from the increased number of red blood cells A similar type of response may be noted in severe anemia as a result of the expression of large quantities of thrombin-rich serum by a greater-than-normal clot retraction

Pathogenesis Intravascular thrombosis begins with the adhesion of thrombocytes to the intima of a blood vessel at a point where the endothelium has been injured, this is followed by the formation of platelet thrombi. The latter are then lysed and thrombin is produced; finally a reticulum of fibrin is deposited. With retraction of the clot, a serum rich in thrombin is expressed, thus causing further local clotting and propagation of the process. Eventually the thrombus fills the lumen of the vessel and causes complete occlusion.

Clinical Picture. SUPERFICIAL THROMBOPHLEBITIS *Symptoms.* In the case of superficial thrombophlebitis, the symptoms are generally minimal and consist of tenderness in the area of involvement. If this happens to be located near a portion of the extremity which is moved on walking, then pain will be felt. No systemic symptoms are experienced

Signs Since thrombosis of a superficial vein does not interfere with venous outflow, there are no signs of increased venous pressure and hence no swelling, except locally in the immediate vicinity of the affected vein. This area generally manifests signs of inflammation, such as redness and increased cutaneous temperature. Palpation of the area reveals the presence of a firm linear mass under the skin, representing the thrombosed vessel and some perivenous inflammation (Fig. 15-27). The lesion may be 1 or 2 in. long or may involve a considerable portion of the main superficial venous channels and their tributaries. Systemic manifestations are not noted.

THROMBOSIS OF DEEP VEINS. The clinical picture associated with thrombosis of the deep veins of the lower extremities will vary markedly, depending upon the importance and location of the occluded vessels and their role in the removal of blood from the limb. If the occlusion involves the venous plexus in the muscles of the calf and plantar portion of the foot (*phlebothrombosis*), little interference with venous return occurs, and hence the physical findings are minimal On the other hand, when a main venous channel, e g, the popliteal or iliofemoral vein, is occluded (*acute deep thrombophlebitis*), the clinical picture is quite typical and apparent.

Symptoms of Phlebothrombosis In this condition, the complaints are rather nonspecific. The patient may be apprehensive and restless, experiencing ill-defined sensations. Locally there may be an ache or a cramplike pain in the calf at rest, with tenderness in this site and in the plantar portion of the foot.

Signs of Phlebothrombosis. One of the more important objective findings in phlebothrombosis is pain in the calf, elicited on dorsiflexion of the foot (*positive Homans' sign*). The calf muscles may be tense or spastic, and at times an indefinite mass may be palpated between the bellies of the gastrocnemius muscle. There may also be a slight increase in the circumference of the calf, determined only by measurement. No obvious swelling is present. Among the systemic signs are slight and simultaneous increases in body temperature and pulse and respiratory rates, without any apparent cause for such changes.

Symptoms of Acute Deep Thrombophlebitis. Typical complaints in this condition are *pain* and *tenderness* along the course of the involved vessel and in the groin. Tenderness is also generally present in Scarpa's triangle. The patient may manifest constitutional responses in the form of malaise and loss of appetite.

Signs of Acute Deep Thrombophlebitis. Because a main venous channel is occluded in acute deep thrombophlebitis, there is marked interference with venous outflow, manifested in the early appearance of *swelling* of the extremity, most obviously in the distal portion (Fig. 15-28). If massive, the edema may resist pitting, but later this type of response may be elicited as the activity of the pathological process diminishes. A common associated finding is the presence of *prominent*

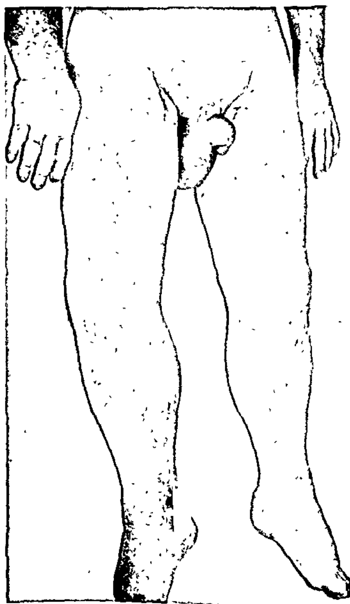


Fig. 15-28. Acute iliofemoral thrombophlebitis of both lower extremities and right axillary vein thrombosis.

and distended superficial veins, particularly on the dorsum of the foot However, in the presence of considerable swelling, this sign may be masked.

If the edema is limited to the foot and leg, the possibility exists that the level of thrombosis is in the popliteal vein. With extension of the swelling into the thigh, it can be assumed that the process is now located in the iliofemoral vein Edema of both lower extremities generally indicates that there has been either occlusion of the inferior vena cava or simultaneous involvement of both iliofemoral veins (Fig 15-28)

Complications. PHLEBOTHROMBOSIS The most serious complication of this condition is *pulmonary embolism.* Because the local phlebitic process in the limb is minimal and because the thrombus may propagate beyond the original site of formation, there is a tendency for portions of the clot to break off and be liberated into the blood stream Another complication is the extension of the thrombus into the main venous channel, producing complete occlusion In a sense, therefore, phlebothrombosis can at times be considered to be an early stage in the development of acute deep thrombophlebitis

ACUTE DEEP THROMBOPHLEBITIS Pulmonary embolism may occur in this condition, but it is seen much less often than in phlebothrombosis This is due to the fact that a phlebitic process is invariably present, so that the thrombus is usually firmly attached to the venous wall at its site of origin A much more frequent complication of acute deep thrombophlebitis is *the postphlebitic syndrome*, which follows prolonged venous stasis resulting from an inadequate collateral venous circulation. The signs which comprise this syndrome are pitting edema subsequently replaced by nonpitting edema, induration and brawniness of the skin, stasis dermatitis, pigmentation, secondary varicosities, and stasis ulcer (Fig 15-27) Subjectively the patient may complain of night cramps and a sense of heaviness and fatigue in the involved extremity Not infrequently the postphlebitic syndrome may be responsible for disabling sequelae which may *restrict* the patient's physical activity for months and even years

Diagnosis. SUPERFICIAL THROMBOPHLEBITIS No difficulty should be experienced in making the diagnosis of this condition. The presence of the local signs and symptoms in the leg and the absence of any systemic response are generally sufficient evidence to lead to the proper conclusion regarding the entity.

PHLEBOTHROMBOSIS. This condition is very difficult to diagnose because of the paucity of localized findings in the extremity. Unfortunately, in most instances its presence is only recognized when a pulmonary embolism occurs

ACUTE DEEP THROMBOPHLEBITIS Because of the obvious findings in the involved extremity, the diagnosis of this condition is readily made. The most important findings are the pain along the course of the involved vessel, the marked swelling of the limb, the prominence of and increased pressure in the superficial veins, and the systemic responses, such as fever of 100 to 101°F, malaise, and loss of appetite

Prognosis. SUPERFICIAL THROMBOPHLEBITIS. This condition is a relatively benign disorder with very few sequelae. Rarely, pulmonary embolism is associated with it Because the vessels involved are part of the superficial venous system, no interference with venous outflow occurs Therefore, sequelae dependent upon venous stasis do not appear If the thrombosis of the superficial veins is secondary to some systemic disorder, then, of course, the prognosis will depend upon the seriousness of the underlying difficulty.

PHLEBOTHROMBOSIS. The local changes in the extremity will in no way affect the efficiency of venous outflow and hence produce no disabling sequelae. However, the appearance of pulmonary embolism will markedly alter the prognosis of this disorder (Fig 15-29)

ACUTE DEEP THROMBOPHLEBITIS If the patient with this condition receives *anticoagulants early* in the disorder and if he is placed on complete *bed rest* with the involved limb *elevated*, there is a good possibility that his subsequent course will be associated with minimal difficulties Physical activity, particularly in the upright and sitting positions, will have to be limited somewhat in order to prevent swelling, but otherwise the patient should be able to lead a normal life Conversely, if the condition is treated incorrectly or if massive thrombosis has occurred, the patient may be left with a very inefficient

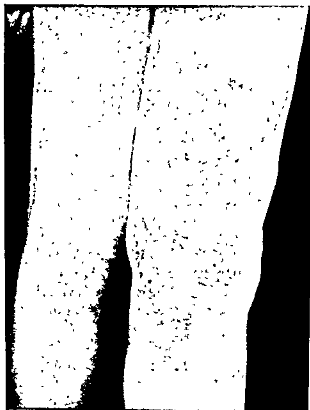


Fig. 15-29. Thrombophlebitis of numerous superficial veins on posterior surface of left thigh and leg (benign superficial thrombophlebitis). (*From Abramson Diagnosis and Treatment of Peripheral Vascular Disorders. Hoeber, 1956.*)

local venous system, which will limit his physical activity for many months or even years. With the appearance of the postphlebitic syndrome, the clinical picture becomes aggravated.

Treatment. SUPERFICIAL THROMBOPHLEBITIS Generally this condition does not require bed rest unless the thrombosed veins are so located that they are stretched with walking and, as a result, pain is caused The usual therapeutic approach is the application of an *elastic bandage* from the foot to above the highest level of thrombosis and instruction to the patient to become ambulatory If the thrombus continues to propagate and appears to be ascending the greater saphenous vein in the vicinity of the fossa ovalis, it is advisable to place the patient on *bed rest, elevate the foot of the bed* and even, at times, administer *anticoagulants*, e g , a combination of heparin and Dicumarol. *Ligation* of the involved vein above the level of thrombosis may at times also be necessary

PHLEBOTHROMBOSIS. In this condition, if the diagnosis is made early enough, *ligation* of the femoral vein below the point of entrance of the deep femoral vein may be performed, provided the exact location of the thrombotic process can be determined. However, it must be pointed out that this approach does *not* invariably prevent pulmonary embolism since, in about 10 per cent of cases, there are venous communications between the femoral vein and the deep femoral vein below the level at which the former is ligated (Edwards and Robuck). As a consequence, emboli arising in the venous plexuses of the calf may still be able to pass through the femoral vein into its communication with the deep femoral vein and then follow the latter into the systemic circulation A better approach to therapy involves the administration of a rapid-acting anticoagulant like *heparin*, together with *Dicumarol*, in order to prevent further propagation of the thrombus into the deep venous system, thus minimizing the probability of liberation of clots into the systemic circulation.

ACUTE DEEP THROMBOPHLEBITIS. In this condition, the patient should be at complete *bed rest*, with the *lower extremities elevated* so as to facilitate venous outflow. The *anticoagulants* should be given at once in order to decrease the tendency toward propagation of the thrombus into the collateral venous channels If there are signs of vasospasm, *wet heat* should be applied for periods of 3 hr, at 1-hr intervals, during the course of the day. The use of *sympathetic blocking agents* is also indicated The patient should remain on this regimen until all edema has disappeared and pain is no longer experienced along the course of the involved vein. Then he is allowed to be out of bed, but only while wearing an elastic stocking fitted for the limb. If, with the onset of the ambulation program, swelling reappears despite the use of compression, the patient should be put back to bed again. Anticoagulants are continued until full ambulation is reached. The *elastic stocking* should be worn until, by trial and error, it is found that compression is no longer necessary to prevent the appearance of swelling and that the patient is comfortable without its use.

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Graphic data in diseases of the aorta and in the peripheral vessels

ALDO A. LUISADA AND EUGENIO JONA

DISEASES OF THE AORTA

Phonocardiogram The phonocardiogram may reveal the following data.

1. An *opening click (or snap) of the aortic valve (ejection sound of aortic valve)*. This is a high and loud group of vibrations which precedes the rise of the carotid pulse by from 0 01 to 0 02 sec. It coincides with the opening of the aortic valve (Fig 15-30A). This phenomenon, described by Lian, and studied by Leatham and several others, causes an apparent splitting of the 1st sound It is due to lesions of the semilunar valves This click, *which is a* part of the 1st sound complex, is larger than the other group of vibrations occurring at the time of AV-valve closure The best frequency range for recording this click is in the 240 to 480-cps band, but there are components of even higher frequency, reaching up to 600 to 1,000 cps The best area for recording this click is the 3d *left* interspace (anatomical projection of the aortic valve), the next best is the *2d right* interspace.

2 A *triple rhythm*, due to addition of a loud systolic vibration (so-called *systolic gallop*). the 1st sound complex is followed by two or more low-pitched, high vibrations, which are simultaneous with the systolic expansion of the aorta (peak of the carotid wave). This rhythm is well recorded at the suprasternal notch (Luisada, 1938, Fig 15-30B).

3. The 2d sound consists of three to four large vibrations and may be prolonged by two or three smaller vibrations equivalent to a *short diastolic murmur*.

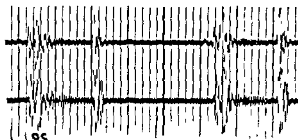
4 A *systolic murmur* is frequently present, its vibrations have the aspect of either a short, early systolic murmur, or of a diamond-shaped murmur. It is recorded best over the 2d or 3d *right interspaces*, but may be loudest at the left of the sternum

According to Aravanis and Luisada, an *early diamond is recorded* if there is a "relative stenosis" due to dilatation of the aorta. In "*obstructive stenosis*," on the other hand, the peak of the diamond is *late* (*late diamond*). An exception seems to occur in children, in whom even obstructive stenosis may have an "early diamond" shape (Nadas) possibly connected with the infundibular type of lesion.

Low-frequency Tracing. The apex cardiogram is of normal aspect or reveals a rapid, high pulsation. There is no slow, staggered rise as in aortic stenosis

Pulse and Pressure Tracings. Pulse tracings reveal a steep rise, a *sharp peak*, and a quick descent. These changes may be due to either aortic insufficiency or increased rigidity of the aortic wall. There is no anacrotic *depression* as in aortic stenosis. The pulse and pressure tracings of the lower extremities frequently reveal an increased pressure. The study of the pulse is particularly significant if the recording is made at the suprasternal notch (Aravanis and Luisada, Fig 15-31).

Atherosclerosis of the aortic arch may cause a smaller pulse and a lower blood pressure in



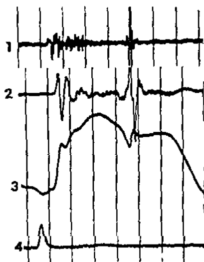


Fig. 15-30. A. Opening click (or ejection sound) (oc) in a patient with atherosclerosis of the aorta and initial calcific aortic stenosis. *Upper*, stethoscopic tracing, *lower*, filter tracing 120 to 240 cps; both over 2d right interspace. B. Low-frequency sound which accompanies the expansion of the aorta in a patient with a dilated atherosclerotic aorta. (1) Medium-high-frequency (120 to 240 cps) phonocardiogram at suprasternal notch showing an opening click and a short systolic murmur (2) Medium-low-frequency (40 to 120 cps) phonocardiogram at same area showing the low-frequency vibration. (3) Pulse tracing at same area (4) ECG

the arms (narrowing of the subclavian arteries). The resulting picture is the reverse of that in coarctation, and may reach its maximum in *Takayasu's syndrome*, or *pulseless disease*, where no graphic tracings are possible on the upper extremities.

Electrokymogram. Both the border tracings and the densograms of the ascending aorta and the aortic arch reveal pulsations of normal or increased magnitude. The pulses have a steep rise, a sharp peak, and a rapid descent. There is no anacrotism in the ascending limb. These data, like those of the pulse tracings, are useful for differential diagnosis in distinguishing other disorders from aortic stenosis.

Atherosclerosis of the Abdominal Aorta

Pulse Tracing; Phonoarteriogram. The tracing of the pulse of the femoral arteries has great amplitude. Its pattern consists of a sharp rise and a rapid drop.

A sound tracing over the 2d right interspace and simultaneously made femoral pulse tracing (or simultaneous pulse tracings of the suprasternal notch and the femoral arteries) reveal *an increased speed of the pulse* in the descending aorta. The femoral pulse normally is simultaneous with the brachial; in atherosclerotic patients, it may precede the brachial pulse.

A systolic murmur is frequently recorded over the abdominal aorta. In patients with an *aneurysm of the abdominal aorta,* the data are similar to those already described in syphilitic aneurysms (Part 9, Chap. 3).

CONCLUSIONS

Graphic data of diagnostic value are (1) a diamond-shaped aortic systolic murmur (phonocardiogram); (2) a large pulse with rapid rise and rapid fall (suprasternal tracing, aortic EKy); and (3) an apex cardiogram with rapid, high pulsation.

These data, together with the electrocardiogram (moderate or absent left ventricular hypertrophy, no bradycardia) are sufficient to exclude aortic stenosis, which might cause a similar systolic murmur.

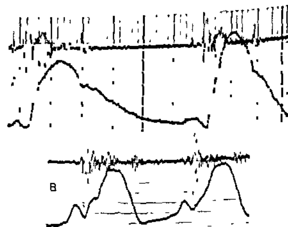


Fig. 15-31. A. Early diamond-shaped systolic murmur, normal aortic pulse (nonobstructive aortic stenosis, atherosclerosis of the aorta). B. Late diamond-shaped systolic murmur; slow rise and anacrotic depression of aortic pulse (obstructive aortic stenosis).

Study of the aortogram will help to confirm the diagnosis of atherosclerosis of the abdominal aorta.

GRAPHIC TRACINGS IN PERIPHERAL VASCULAR DISEASES

These tracings reveal the level of pressure in the various arteries, the amplitude of their pulsations, and the configuration of the pulses.

The most varied findings can be obtained In certain cases, *no pulse tracing* (and no indirect pressure tracing) can be obtained over certain arteries This is usually due to occlusion of the vessels However, *extreme narrowing of an artery* may still allow a thin, continuous flow of blood which cannot be appreciated from these tracings because of the absence of pulsation. A similar phenomenon may be observed in coarctation of the aorta (lower extremities only), as well as in aortic stenosis, shock, or congestive heart failure (all arteries) In cases of embolism, *absence of pulsations* below a given point is suggestive of arterial occlusion.

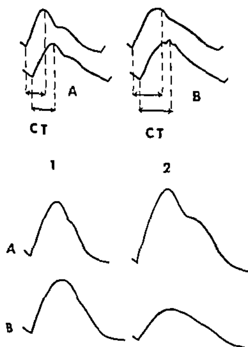


Fig 15-32. Upper Radial and digital pulses A, normal, B, peripheral arteriosclerosis, CT, crest time. Lower Changes in the arterial pulse of the lower extremities (1) before and (2) after exertion A, normal, increased amplitude, B, arteriosclerosis obliterans, decreased amplitude.



Fig 15-33. Phonoarteriogram and pulse tracing of a traumatic arteriovenous fistula at the groin Continuous murmur with systolic increase.

Senile arteriosclerosis is accompanied by changes in the configuration of both radial and digital pulses. In patients with this disease, *crest time* is markedly increased in both radial and digital tracings (Fig. 15-32, upper part). Younger persons with initial arteriosclerosis may also reveal an increase of the crest time of the digital pulse. It has been also noted that, in arteriosclerosis, the dicrotic waves decrease sharply and may disappear in the tracings of the fingers and toes.

Pulse and pressure tracings can be recorded before and after exertion Patients with organic arterial disease, with or without intermittent claudication, present an inverse reaction with decrease of blood pressure and smaller pulses in the lower extremities (Fig. 15-32, lower part).

In *arteriovenous fistula*, a normal (or high) systolic and a low diastolic pressure are observed. Pulse pressure is markedly increased; the pulse wave has an increased velocity. The predicrotic notch may be at a low level The arterial pulse may be weak and even disappear below the fistula.

Phonocardiogram. A sound tracing recorded *over the abdominal aorta* frequently reveals a systolic murmur in peripheral vascular diseases This murmur is probably due to the association of atherosclerosis of the abdominal aorta with obstruction of flow in the iliac or femoral arteries

In *arteriovenous fistula*, sound tracings reveal a continuous *murmur* with vibrations of both high and low pitch. The vibrations are larger during the expansion of the artery, smaller during its collapse (Fig. 15-33). The two phases coincide with ventricular systole

and diastole if the fistula is near the heart; they are delayed beyond these phases in more peripheral vessels.

The sound tracing has been used in differential diagnosis to exclude an arterial aneurysm compressing the veins. Such an aneurysm usually presents no audible diastolic murmur. However, the sound tracing may reveal minute diastolic vibrations, especially if there is aortic regurgitation Whenever the fistula is within the chest (aorta to superior vena cava), the murmurs increase during inspiration.

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Surgical treatment of peripheral vascular diseases

Surgery of Venous Disorders

Surgery of Occlusive Arterial Diseases

R. B. LYNN

SURGERY OF VENOUS DISORDERS

Just as in occlusive arterial diseases, the surgery of venous disorders is virtually confined to affections of the veins of the lower extremities The conditions amenable to some form of surgical intervention are varicose veins, early deep-venous thrombosis, and the post-thrombophlebitic syndrome These diseases may complicate pregnancy or be associated with systemic disorders such as cardiac failure, atherosclerosis, diabetes, and obesity If this is the case, then the management of the associated condition may take precedence over the venous disorder, or its control may be necessary to ensure successful surgery. Thus, surgical and medical measures must be combined to ensure the patient the best results.

VARICOSE VEINS

Primary varicose veins and secondary or "compensatory" varicose veins, which provide additional embarrassment to the venous return in the postphlebitic limb, tend to progress if not treated The complications of untreated varices are varicose eczema or dermatitis, ulceration, hemorrhage, thrombophlebitis and, rarely, malignant degeneration in a varicose ulcer Most patients, however, first appear not with a complication but with vague complaints of aches, tiredness, and swelling, and their chief reason for seeking treatment is that the veins are unsightly. If conservative management of varicose veins, primarily by elastic support, is put aside, then the surgical measures available are sclerosant therapy and operative extirpation.

Sclerosant Therapy. The local injection of a chemical irritant into varicose veins is over 100 years old. The success of the method depends upon the careful selection of patients and the use of a substance which severely damages the intima of the vein and so produces obliteration of the lumen by formation of an organized thrombus. The best application of sclerosant therapy is in the treatment of localized varices which recur or remain after an adequate high ligation and stripping operation. Localized varices of the "vanity" type, and those associated with competent valves in the saphenous and communicating veins, complete the indications for injection treatment. Contraindications are previous deep thrombosis, severe occlusive arterial disease, and debilitating diseases, i e, in cardiac patients, where extensive thrombosis may ensue because of the associated circulatory stagnation. Injections into asthmatic patients must be administered with great care, as fatal allergic reactions have been reported

Although more than 20 substances have been recommended, the author uses only 0 5 to 2 0 ml of 5 per cent monoethanolamine oleate This soapy substance is a nontoxic, effective endothelial irri-

tant in the above dosage. The only equipment needed is a 2.0-ml syringe, a 1½-in. No 20 short-bevel needle, and sterile dressings. A tourniquet is not necessary. The vein is marked and the skin cleansed with tincture of iodine while the patient sits dangling the leg. The physician uses the "empty vein" technique, once the vein has been entered, the patient lies down and, after the position of the needle point has been rechecked by aspiration, 0.5 to 2.0 ml of the chemical is slowly injected. Emptying the vein ensures maximum local concentration and prolonged contact with the intima. After patient has been lying still for 10 min, a pressure pad is applied over the injection site, and full ambulation is resumed.

The incidence of pulmonary embolism after sclerosant therapy is about 1 in 15,000 cases but increases to 1 in 3,000 cases if prolonged rest is advised, since this leads to excessive thrombosis and spread to the deep venous system. This fact, too, emphasizes the danger of sclerosant injections when incompetent communicating veins are present. If repeated injections are needed they are administered at fortnightly intervals

Complications after injections should be rare if small volumes of irritant are used and the patients are carefully selected. Extensive thrombosis may occur, with spread to the deep veins, and, rarely, pulmonary embolism. Sloughing of the skin and an injection ulcer may follow extravasation or inadvertent injection of the chemical into the perivenous tissues These two complications are avoided by careful injection and the immediate cessation of injection if the patient complains of local pain or cramp in the calf of the leg. Suppurative phlebitis and local infection are rare. Recurrence of varices after injection is common, and when the recurrence is rapid a missed incompetent communicating vein, better treated surgically, must be suspected.

Surgical Measures. When the saphenofemoral valve is incompetent, with or without incompetent communicating veins, operative treatment is necessary for cure The operation of choice is high, "flush" saphenous ligation combined with stripping of the long saphenous vein, or short saphenous vein or both, from the ankle to the groin. Stripping of varicose veins is now 50 years old and has grown and declined in favor since it was introduced by Mayo. The indications for high saphenous ligation and stripping are (1) definite varices, (2) a history or presence of a complication, e.g., stasis ulceration or dermatitis; (3) the presence of combined deep and superficial insufficiency when it is proved that the superficial varices are adding to the venous stagnation in the limb; and (4) the presence of gross varices, in which case the process is prophylactic against complications. Contraindications include (1) pregnancy; (2) severe cardiovascular or renal disease; (3) severe occlusive peripheral vascular disease, (4) recent acute deep or superficial thrombophlebitis; (5) uncontrolled or infected stasis ulcers, and (6) uncontrolled metabolic disorders, e.g., diabetes, obesity.

Operative Techniques. If high saphenous ligation alone is to be performed, local anesthesia is preferable but, when stripping is desirable as well, as it is in most patients, the operation is performed under light general anesthesia. The supine patient is placed in a 10° Trendelenburg position to prevent venous stagnation; then the affected leg is allowed to externally rotate. The patient's previously shaved groin is carefully cleansed with soap and water or Cetavlon and then painted with tincture of iodine; the vulva or scrotum is avoided. A 5-cm vertical incision is made, this is centered 1.5 cm below and 2.5 cm lateral to the pubic tubercle and just medial to the femoral artery, which must be palpated. The vertical incision follows one of the first principles of vascular surgery, i.e., that the incisions for a vessel should be in the line of the vessel, this affords better exposure especially in the obese patient, prevents unnecessary mobilization of flaps which leads to hematoma formation and infection; and avoids division of inguinal lymphatics, thus preventing postoperative lymphorrhea and exacerbation of edema, which is especially important in the postphlebitic limb

The incision is deepened to expose the fossa ovalis, a selfretaining retractor is inserted, and, by means of blunt dissection, the termination of the saphenous vein and its tributaries are visualized. These branches are subject to wide variation and the surgeon is advised to rely upon an adequate exposure and complete dissection of the region, rather than upon classical anatomical descriptions, so that no tributary will be missed. Each branch (usually six in all) is carefully exposed, doubly ligated, and divided. After all the branches have been treated the saphenous vein is divided, at the distal end of the incision, and lifted upward so that the saphenofemoral junction can be clearly

visualized Clamps are never placed on the vein in this region The vein is now ligated flush with the femoral vein by means of No. 0 braided silk, and as insurance, a transfixion suture is placed 0.5 cm distal to it. The distal end of the vein is triangulated, and a malleable intraluminal stripper passed downward to the ankle, here a 2-cm incision is made, again vertical to avoid damaging the saphenous nerve, just in front of the medial malleolus. The termination of the long saphenous vein is located there, in the groove between the anterior border of the malleolus and the tibialis anticus tendon. The vein is tied distally with No. 00 plain catgut. The proximal end of the vein is doubly tied to the stripper with a 3-ft piece of No. 2 silk and then avulsed with a slow, steady pull If the stripper pulls off the vein, or if the vein inverts or breaks off, it can be retrieved and removed without additional incisions by means of the long silk thread. Often it is easier to pass the stripper upward from the ankle to the groin, and when this is done additional incisions are often necessary either to control large "blowouts" or when the veins are excessively tortuous As the vein is removed, pressure is exerted over the course of the stripped vein, and the leg is elevated to minimize hematoma formation. The incisions are closed in layers and a toe-to-groin elastic bandage applied. The patient is ambulatory that evening and leaves the hospital in 3 to 5 days

The short saphenous vein is varicose alone or together with the long saphenous vein in about 10 per cent of patients The short saphenous vein is visualized where it plunges into the popliteal fossa through a 5-cm transverse incision in the superior crease over the fossa It is seldom necessary to follow the vein to its junction with the popliteal vein since it rarely has branches entering it deep to the fascia of the fossa The short saphenous vein is doubly ligated proximally and then may be simply ligated distally after resection of a segment, or a stripper may be passed downward and picked up through a vertical incision just in front of the tendoachillis, 5 cm above the lateral malleolus The vein may then be stripped out, after this the incisions are closed and a pressure bandage is applied

The surgery of varicose veins is a major procedure and should only be performed by well trained, interested surgeons in a well-equipped operating room. Hemorrhage from torn tributaries or a torn femoral vein is the commonest complication and is best controlled by packing followed by enlargement of the incision to obtain proximal and distal control of the torn vessel, which can then be repaired. Blind clamping can cause further damage and must never be employed. Hematoma formation and infection are uncommon unless the operation is performed in the presence of an uncontrolled ulcer. The femoral artery has been torn, ligated, transected, and even injected. Deep venous thrombosis and pulmonary embolism (0 5 per cent of patients) may occur, but is now rare since injections are no longer combined with the surgical procedure. Some swelling of the ankle and lower leg may follow stripping but this is easily controlled by the wearing of elastic bandages or stockings for a few weeks and must not be allowed to interfere with the patient's activities. Occasionally, the saphenous nerve is damaged and the patient complains of paresthesia or even anesthesia over the inner side of the foot and ankle. This is usually temporary Recurrences are rare indeed and may be dealt with by postoperative injections in most patients, although occasionally the additional ligation of a "blowout" may be necessary High saphenous ligation and stripping gives an initial cure rate of over 90 per cent and is the procedure of choice in all superficial varices of the legs.

THROMBOSIS AND EMBOLISM

There is little place for surgery in the management of *deep-venous thrombosis* Some years ago, *prophylactic ligation of the superficial femoral veins* was advocated to prevent subsequent thrombosis and pulmonary embolism It soon became obvious that prophylactic proximal ligation not only did not reduce the number of fatal emboli but was also followed by chronic edema, ulceration, and all the features of a postphlebitic limb. Prophylactic *deep-vein ligation* is rarely, if ever, indicated

Proximal vein ligation has been advocated in established thrombosis, particularly when pulmonary embolism has occurred. Others still advocate it as a means to prevent *pulmonary embolism* after thrombosis has developed There is no real evidence, however, that such ligation is followed by a lower incidence of pulmonary embolism than would be expected

if the patient received good anticoagulant therapy. Usually, the femoral vein is explored through a vertical incision, similar to that used for high saphenous ligation, and the superficial femoral vein is exposed, then tapes are placed around it and its wall incised. Loose clot, if present, is sucked out, and then the vein is ligated distad to the profunda vein. Repair of the vein wall without ligation has been advocated when the operator feels sure he has removed all of the clot. If the common femoral vein is ligated, crippling edema is frequent. The criticisms of this procedure are that (1) it does not prevent emboli from arising proximally; (2) it cannot always be determined from which side the embolus came; and (3) not infrequently incision of the vein shows it to be filled with adherent clot so that it is obvious that a much more proximal ligation is necessary if the dubious principle of the procedure is to be justified. The only logical procedure to prevent all embolism is *inferior vena caval ligation*, and this crippling procedure is not to be lightly advised (Shea) If it is necessary, the approach is the same as that for a right lumbar sympathectomy The only indications for proximal deep vein or inferior vena caval ligation are (1) repeated pulmonary emboli not controllable by any other means, (2) nonavailability of adequate supervision of anticoagulant therapy, or (3) contraindication of anticoagulant therapy by the coexistence of other diseases or states, e g., hemorrhage from the gastrointestinal tract, some blood dyscrasias, jaundice, or severe renal or hepatic disease

Rarely, the *long saphenous vein is ligated* when superficial thrombophlebitis, which complicates varices, progressively ascends the thigh in spite of therapy. Fatal *pulmonary embolism* has occurred under such circumstances, and high saphenous ligation should be advised for progressively ascending superficial thrombophlebitis and performed under local anesthesia by the technique described above.

THE POSTTHROMBOPHLEBITIC SYNDROME

One of the consequences of a deep venous thrombosis is later recanalization of the formerly thrombosed vein; and with recanalization there is destruction of the venous valves. When this happens the usual reduction of pressure which occurs when the patient walks does not occur, and unremitting elevation of venous pressure develops in the limbs This leads to venous and capillary stagnation, which ultimately goes on to orthostatic edema, pain, pigmentation, dermatitis, and ulceration of the leg, which may or may not exhibit compensatory varicose veins. The original deep-venous thrombosis may have occurred so many years previously as to have been forgotten. Indeed, proof of a previous deep thrombosis is often completely lacking. When the postphlebitic syndrome is fully established, it may be treated conservatively or by a variety of surgical measures.

Nonsurgical Treatment. At least 90 per cent of postphlebitic limbs can be maintained in a good state of nutrition and their ulcers kept healed by means of a conscientous conservative regimen. The only part of any conservative treatment that is of the slightest importance is properly applied *elastic compression* This has been recognized for about 200 years, and still remains the most important part of any surgical treatment as well, although it is often not credited by various authors championing their favorite operation.

Elastic compression is best maintained by a strong, one-way-stretch elastic bandage applied before the patient gets out of bed in the morning and worn all day The bandage may have to be removed at intervals for readjustment or for dressing the ulcer Modern elastic stockings are not adequate to maintain firm elastic support. Unna's paste boots still have a place in treating the elderly, the debilitated, or those who cannot or will not use elastic bandages When it is available, physical therapy in the form of the Bisgaard routine may be added to the treatment A variety of nostrums has been advocated for healing these ulcers. The only necessary feature of such medicaments is that they shall do no harm, as none will heal an ulcer without elastic support. Modifications of Luke's "new way of life" are a necessary adjunct to the management of the patient.

Surgical Treatment. The surgical measures advocated for the relief of the postphlebitic syndrome are (1) *ligation* and *stripping* of compensatory superficial varices; (2) radical excision of the ulcer and associated varices, with or without skin grafting; (3) deep vein ligation alone or in combination with pro-

cedure (1) or (2) or both; and (4) lumbar sympathectomy.

Compensatory varicose veins are best eradicated by high saphenous ligation and stripping as described above This is done only when (1) the patient's general condition warrants it, (2) the ulcer (if present) is clean and controlled by elastic compression; and (3) it has been shown by the walking test that the deep veins are not obstructed Venography may be of value here This is the most frequently performed surgical procedure for the postphlebitic limb, and once the venous-lymphatic stasis has been improved by superficial vein surgery elastic compression will maintain the improvement.

Radical surgery is seldom necessary in the postphlebitic limb as even the worst-looking ulcer and the most scarred and indurated leg will heal with patient application of conservative measures. In a small number, probably 2 to 3 per cent of patients, the ulcer may seem indolent, malignancy may be suspected, or the patient, surgeon, or both become impatient, and radical surgery is advised. There is, however, no surgical procedure which alone will maintain healing in the surgically corrected leg without permanent postoperative elastic compression The radical operations employ long incisions to include the ulcer at the ankle and so excise all the dense scar tissue in and around the ulcer, but primarily they excise completely the incompetent communicating veins invariably present in the ankle region of the postphlebitic leg Once this excision is complete, it may be necessary to cover the excised area with a split-thickness skin graft Permanent postoperative elastic support to the limbs is necessary to prevent recurrence of ulceration, in spite of radical surgery

Deep vein ligation in the plostphlebitic syndrome was first advocated by Homans (1937) and later championed by Bauer (1955) and Linton (1953b). It has been clearly shown that ligation of the superficial femoral vein (Homans, Linton) or the popliteal vein (Bauer) actually increases venous stasis in the limb and the author cannot recommend these procedures. The author has tried and discarded these irrational methods because they neither influence ulceration nor improve edema, indeed they often make it worse, and only occasionally do they relieve pain in the limbs. This uncommon "bursting" type of pain can be equally well controlled by adequate elastic support, without the disadvantages of interrupting an important blood vessel It is unfortunate that venography ever showed retrograde flow in postphlebitic limbs, as reflux occurs almost as often in the normal limb. If retrograde venography had not been so often misinterpreted, many ligated veins would still be performing a useful (albeit impaired) function and carrying blood back to the heart.

Sympathectomy has an even smaller place in the management of the postphlebitic limb than has radical surgery It will never heal and maintain healing in an ulcer without ancillary measures *Lumbar sympathectomy* should be restricted to the occasional postphlebitic limb which has a superimposed occlusive or vasospastic vascular disease, e g, atherosclerosis, hyperhidrosis, or chilblains In patients with such "combined" ulcers, lumbar sympathectomy will enhance nutrition and abolish sweating, as well as the often troublesome dermatophytosis which develops on the macerated hyperhidrotic foot. Even so, prolonged elastic support is necessary to prevent recurrence Since the main problem in the postphlebitic limb is venous stagnation, and since lumbar sympathectomy will only increase arterial inflow and so place an additional burden on lymphatic and venous return, the procedure is generally contraindicated in chronic deep-venous incompetence.

SURGERY OF OCCLUSIVE ARTERIAL DISEASES

It should be emphasized that far more patients with occlusive disease of the peripheral arteries are treated by conservative than by surgical means and that many surgical procedures will fail unless combined with the so-called "conservative" measures Thus, protection of the ischemic limb from trauma, avoidance of undue heat or cold, weight reduction, correction of anemia and diabetes, and the absolute cessation of smoking, are some factors which, if controlled, will ensure that the moderate but important part that surgery has to play is given the best chance of success

The main objectives of surgery in occlusive

arterial diseases are (1) *improvement of the nutrition* of the ischemic limb by increasing its blood supply; (2) *the relief of intermittent claudication;* and (3) *amputation* of gangrenous tissue when all other forms of treatment fail. There are three major occlusive diseases to which these objectives are applied: atherosclerosis, thromboangiitis obliterans, and Raynaud's disease. By far the greatest number of candidates for surgery suffer from atherosclerosis (with or without associated diabetes), 90 per cent in the author's experience.

Current interest is centered upon the technical aspects of the surgical measures available for relief of obliterative arterial disease and, because of this, there is a prevailing impression that the majority of patients are eligible only for one certain surgical procedure. Accordingly, the author has chosen to emphasize the selection of patients and the indications for the various procedures available to the surgeon. The intimate technical details of the surgical methods will not be stressed, as they are readily available in texts on surgical methods.

METHODS OF INCREASING PERIPHERAL BLOOD FLOW

The blood supply to an ischemic limb may be increased by direct or indirect surgery. *Indirect surgery,* in the form of lumbar or cervicodorsal sympathectomy, still remains the operation of choice in peripheral occlusive vascular disease (Smithwick, 1957). *Direct surgery,* in the form of arterial reconstruction, is the method of choice when more proximal major vessels are the seat of disease, e.g., aorta and iliac arteries. It must be appreciated that obliterative arterial diseases are generalized, and the whole patient must be considered, not just the limb Thus, complete investigation of the cardiovascular status of each patient must precede surgery because of the frequent association of peripheral vascular disease with coronary, cerebrovascular, and renal diseases There is little point in subjecting a patient to a major operation only to convert him into a cardiac cripple from precordial pain which was masked by the reduced exercise tolerance consequent to claudication

Sympathectomy. There is conflicting evidence on the importance of the sympathetic innervation of skeletal muscle in man It can be stated, however, that release of vasoconstrictor tone of muscle arteries by sympathectomy is of little importance and has little effect on the vessels of limbs with claudication Thus, sympathectomy must not be offered to the patient *solely* for the relief of intermittent claudication, as it will not relieve the pain arising from muscle activity except in the rare case of isolated high major vessel block (which is now best treated by direct surgery). *Lumbar and cervicodorsal sympathectomy are indicated when ischemia of the skin, with or without minor ulceration or gangrene, is present* Coldness, paresthesia, and rest pain are often dramatically relieved by sympathectomy. Similarly, in a properly selected patient, ischemic ulcers may heal and local gangrene may be restricted. Also, if cutaneous blood flow and nutrition are improved, a major amputation may be avoided. Age is no contraindication if other factors are favorable—the author has successfully relieved ischemic ulceration in an 86-year-old woman by performing lumbar sympathectomy.

Certain preoperative tests are necessary before any patient can be selected for sympathectomy. The use of sympathectomy in a "let's see what will happen" manner has unfortunately brought this most valuable procedure into disfavor in many centers. The results of sympathectomy in the treatment of occlusive vascular diseases of the limbs are dependent upon the care with which patients are selected for surgery. Before sympathectomy can be advocated, it is necessary to demonstrate a definite release of vasomotor tone by means of reflex heating, paravertebral or peripheral nerve block, or the intraarterial injection of a vasodilator drug. The degree of release of vasoconstrictor tone is measured by cutaneous temperature responses or, preferably, by plethysmography (Part 4, Chap 3). These methods are not infallible and more than one test always must be made. The degree of response is an index of the ability of the ischemic tissues to dilate in response to sympathetic denervation. In virtually all cases of obliterative vascular disease, delineation of the vessels by *arteriography* is advocated. This technique enables the surgeon to exclude the patient who might be suitable for arterial reconstruction and also to recheck release of vasoconstrictor tone when the patient is under anes-

thesia. If the patient is selected for sympathectomy, lumbar sympathectomy will be performed for occlusive arterial disease of the legs, cervicodorsal sympathectomy if the arms are involved

LUMBAR SYMPATHECTOMY. The lumbar sympathetic chains lie on the anterolateral aspects of the vertebral column along the medial edges of the psoas muscles The lumbar vessels usually lie behind the chains but, not uncommonly, on the right the veins in particular lie in front of the chain. The right chain and ganglia are overlapped by the inferior vena cava and the left chain lies just lateral to the aorta. Four lumbar ganglia are usual, five or more are uncommon, and in exceptional cases there may be only one or two. Asymmetry of the two sides is normal and the positions, sizes, and shapes of the ganglia are inconstant. They may be unequal in size and elongated or flattened in shape Removal of the second and third ganglia and the intervening portion of chain will denervate the leg below the knee but, if denervation of the leg to the groin is desired, the first ganglion must also be removed Because of the anatomical irregularities in the chains, it will be appreciated that such precise removals are impractical. Accordingly, *it is the author's practice to remove the entire lumbar sympathetic chain from the brim of the pelvis to (and including) the ganglion which lies under the crus of the diaphragm* This ganglion is most probably always the first lumbar ganglion and is constant in site and shape, in that it resembles a Scotch thistle because all its rami enter and leave it superiorly Sterility in the male from bilateral removal of both first lumbar ganglia is not invariable and, if a complete sympathectomy is desired, both first lumbar ganglia must be removed, otherwise the collateral vessels around the block will not be denervated

Technique. General anesthesia augmented by muscle relaxants is the anesthetic procedure of choice Spinal anesthesia should not be used because there is danger of hypotension and the concomitant ill effects of compensatory vasoconstriction in the unanesthetized upper half of the body including the coronary arteries With the patient slightly flexed and lying in a semioblique position on the opposite side, a 10-cm transverse incision is made This extends from the tip of the twelfth rib to the lateral border of the rectus muscle The incision is deepened to the external oblique muscle which is split along the line of its fibers The internal oblique and transversus muscles are similarly split along the lines of their fibers to expose the peritoneum Beginning at the posterior end of the incision, the peritoneum is reflected forwards and medially together with the ovarian or testicular vessels and the ureter. The psoas muscle with the genitofemoral nerve on its surface is thus exposed and the lumbar chain will be seen (sometimes, in fat subjects, more easily felt at first) at its medial edge under the inferior vena cava, on the right side and lateral to the aorta on the left. After these structures have been gently retracted medially, the chain is picked up with a blunt hook and all its communications are divided with scissors Special care must be taken to recognize the lumbar vessels which may occasionally lie in front of the chain, particularly on the right side; where this occurs the chain must be carefully drawn under them The chain is followed down to the brim of the pelvis and then up to the crus of the diaphragm, which is split to expose completely the first lumbar ganglion; this is recognized by the oblique entry of all its rami from above The chain is avulsed above the first ganglion If this procedure is followed, at least 10 cm of chain and ganglia will be routinely removed. The muscle layers are then loosely approximated with catgut and the skin closed with silk There is no need for drainage and, if the operation is performed under general anesthesia with relaxants, it should not take more than 10 min When there are signs of ischemia in the opposite limb, it is the author's practice to remove both lumbar chains at one operation. The muscle splitting incision is preferred to muscle cutting because of its simplicity, its anatomical soundness and, most important, its avoidance of all blood vessels It is rarely necessary to apply a hemostat during the operation.

Although this is the standard operation, it may, on rare occasions, be necessary to use the transperitoneal route, e.g, in a patient with aortic thrombosis not suitable for excision and grafting. The chains are approached through a midline abdominal incision to avoid all the collateral vessels which may be participating in the blood supply to the legs The right chain is found behind the peritoneum, below and to the left of the root of the mesentery and medial to the ureter. The left chain is revealed by reflecting the descending colon and splenic flexure medially. It is difficult and often impossible to remove the first lumbar ganglion when this approach is used.

The mortality rate for lumbar sympathectomy is negligible, and the operation can be tolerated by patients up to 86 years of age. The side effects are (1) *anhidrosis* of the denervated extremity, (2) variable *sterility* in the male if both first lumbar ganglia are removed, (3) compensatory *sweating* in the normally innervated half of the body—this is a problem only in warm climates, and (4) the *postsympathectomy syndrome.* The latter commences

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Fig. 15-34 Horner's syndrome.

as a discomfiting, deep-seated, gnawing pain in the thigh, it is worse at night and is frequently accompanied by hyperesthesia of the overlying skin and quadriceps wasting. Although the exact source of this pain is not certain, it is probably due to degeneration of the white rami communicantes connecting with the first, second, and possibly the third lumbar spinal segments. The pain always disappears within three weeks to three months and is best controlled by analgesics. Physical therapy in the form of heat and quadriceps drill is sometimes helpful.

CERVICODORSAL SYMPATHECTOMY. Denervation of the upper extremity is less satisfactory than denervation of the leg and is always followed by some degree of return of vasoconstrictor tone, a complication which never follows lumbar sympathectomy. This is primarily due to the variability of sympathetic outflow to the upper extremity and the existence of intermediary ganglia. The preganglionic outflow in man is primarily from the second to seventh thoracic segments, inclusive. After ascending in the gangliated chain, the major relay is in the *stellate ganglion*. (In 80 per cent or more of subjects, the inferior cervical and first thoracic ganglia are fused to form the stellate ganglion.)

The stellate ganglion is creamy pink, 1.5 to 2.5 cm long, and irregular in shape, it derives its name from the radiation of branches from it. It lies anterior to the neck of the first rib and the eighth cervical transverse process, and medial to the superior intercostal artery and vein. The vertebral vessels lie close to its superior pole and the subclavian artery lies immediately anterior to it. The ganglion lies posterior to the apex of the lung which is often thickened by a musculoaponeurotic slip from the scalene muscles which forms Sibson's fascia. The stellate ganglion is connected to the second thoracic ganglion which lies on the neck of the second rib.

The second ganglion is the key ganglion, as its removal alone will lead to preganglionic denervation of the arm in nearly every patient (although more extensive sympathectomy is desirable). However, removal of the stellate ganglion is invariably followed by *Horner's syndrome* and this complication, particularly when unilateral, is unsightly (Fig. 15-34). The best procedure for complete denervation of the upper extremity is removal of the stellate, second, and third thoracic ganglia, but most surgeons and patients prefer to compromise and leave the stellate ganglion intact and so prevent (1) Horner's syndrome, (2) nasal obstruction from hyperemia of the nasal mucosa, (3) excessive dandruff due to the anhidrosis, and (4) occasional gustatory sweating. The advantages of a slightly longer period of freedom from return of vasomotor tone after a cervicodorsal sympathectomy which includes the stellate ganglion are outweighed by the disadvantages outlined above since some degree of return of vasomotor tone is invariable regardless of the operation. It is now recognized that there is no practical clinical advantage of pre- over postganglionic resection, so this problem will not be mentioned further.

Technique. The anterior operation is the simplest and least traumatizing and it has the advantage that bilateral sympathectomy can be safely accomplished in one operation. Axillary and posterior approaches are described but have no advantages over the anterior route and possess very real disadvantages.

Under general anesthesia, the patient is intubated in case the pleura is inadvertently opened and a small sandbag is placed between his scapulas, his head is turned to the opposite side, and his arm is pulled downward to open up the supraclavicular space. A 3-in. incision is made, beginning over the inner border of the clavicular head of the sternomastoid muscle 2 cm above the clavicle and running laterally. The platysma muscle is divided along the line of the incision. The external jugular vein, which is in the outer angle of the incision,

can be retracted The clavicular head of the sterno- ... from its insertion The ... tissue over- ... may be divided. By means of gauze dissection the scalenus muscle will be exposed with the phrenic nerve running downwards and medially across its surface The nerve is mobilized and retracted medially with a tape. The edges of the scalenus muscle are defined and the subclavian artery will be seen emerging from beneath its outer border The insertion of the muscle into the first rib is nibbled through while the artery is protected from behind by a right-angled clamp or malleable spatula. If the muscle substance is cut into, troublesome bleeding occurs Once the scalenus is completely divided, the first and second parts of the subclavian artery come into view. In cases of occlusive vascular disease, the operation should be continued by approaching the chain from below the subclavian artery, since no branch of the subclavian artery must be divided, it might be an important collateral The neck of the first rib is felt for, and the apical pleura can usually be elevated from the necks and adjacent shafts of the upper three ribs by finger dissection Occasionally, it is necessary to incise the apex of Sibson's fascia. The superior intercostal artery and vein must be avoided because, if they are torn, they can be the source of troublesome bleeding, this is best controlled by coagulation or packing It is convenient to depress the apex of the lung with a lighted retractor. The chain should now be readily felt and seen running downward and backward It is divided distal to the third thoracic ganglion and dissected upward, thus dividing all the rami to the third and second ganglia The cut end of the chain is then stitched to the cut end of the scalenus anticus muscle to delay regeneration If the stellate ganglion is to be removed, it is easily freed of all its divisions and the cervical chain is cut above it The stellate ganglion is, however, usually left intact Once the sympathectomy of choice has been completed, the incision is filled with saline solution and the anesthetist inflates the lung Thus, an inadvertent pneumothorax may be detected and evacuated The incision is closed in layers without drainage by approximating the clavicular head of the sternomastoid muscle, the platysma muscle, and the skin If surgery of both sides is to be performed, the patient's head is turned to the other side and the above procedure repeated

The mortality rate is negligible but the results of cervicodorsal sympathectomy are inferior to those of lumbar sympathectomy because of the degree and inevitability of return of vasomotor tone

Arterial Reconstruction. The best method of increasing the peripheral blood flow is to remove the offending obstruction and so permit unrestricted blood flow to the extremity. Two methods are available for this: (1) thromboendarterectomy, and (2) blood-vessel grafts (artery, vein, or fabric). Perusal of the current literature leaves one with the impression that most patients suffering from occlusive vascular disease are suitable candidates for restorative surgery. This is far from the truth, especially when the disease is in the legs, less than 15 per cent of the cases seen by surgeons can be accepted Even this figure is inflated because of prior selection before referral to the surgeon. The number of suitable patients is higher when the disease involves the aorta and iliac vessels but here, too, the success of the procedure depends upon the peripheral vessels being free from disease, which they seldom are. Thus, *arteriography* or *aortography* must precede any direct surgical attack on an obliterated artery. The most important points to be determined are the size, the patency, and the state of the distal vessel wall The best results will follow aortic and iliac occlusions Limited success will follow femoral artery surgery and it is only in an exceptional case that a good result follows direct surgery on more distal vessels. Patients with claudication alone should not be subjected to these procedures unless the pain is so severe that they cannot work. On the other hand, when rest pain or ... tomical feat ... is advised ... harm can follow an unsuccessful graft or disobliteration because the alternative is amputation of the limb Strict selection is the key to success in any direct surgery

THROMBOENDARTERECTOMY. This operation is possible in less than 1 per cent of patients with occlusive arterial diseases of the extremities. It is of no value in *Buerger's disease* because of the nature of the arterial disease in thromboangiitis obliterans, obliteration of small arteries is the rule and obstruction of a major artery uncommon. Arteriography is necessary, and a well-localized obstruction in a vessel free from calcification is essential for success (Fig 15-35). Originally long segments were obliterated, but initial success was followed by early thrombosis and recurrence of symptoms.

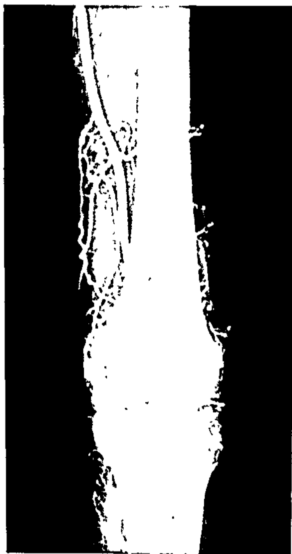


Fig. 15-35. Wasp-waist constriction of popliteal artery, free from atheroma and ideal for endarterectomy.

Better results are obtained in the iliac vessels, but here grafts are preferable except in the case of local obstructions (Fig 15-36).

Technique. The principle of thromboendarterectomy is to remove the obliterated segment through a plane of cleavage in the media Thus the atheromatous plaques and thrombus are removed along with the intima and media out to but not including the external elastic lamina The adventitia and the outer layer of the media remain as the vessel wall. Although the remaining artery wall is attenuated it is capable of withstanding the arterial blood pressure without aneurysm formation. Long-term anticoagulant therapy, for years if necessary, will ensure that recurrent thrombosis is rare.

The artery is exposed through a long skin incision overlying the thrombosed segment A longitudinal incision is made into the vessel wall after establishment of proximal and distal control of the patent portions of the vessel by means of bulldog clamps Careful blunt dissection with a MacDonald dissector will develop a plane of cleavage in the media. The thrombus can then be easily stripped up and down the vessel. Bleeding from collaterals is controlled by means of small bulldog clamps. Once the offending thrombus is removed, the intima of the proximal and distal portions of the vessel must be stitched to the vessel wall in order to prevent dissection and thrombosis. The vessel wall is carefully sutured with No 00000 arterial silk and the clamps are removed. Multiple short incisions may be made, rather than a single long one, and special strippers may be used to mobilize the thrombus, but when this is done there is an implication that too long a segment is being disobliterated The incision is closed without drainage and heparin is started 6 hours postoperatively. Long-term anticoagulant therapy is commenced the next day with a Dicumarol derivative and is continued for months or years to minimize recurrent thrombosis

BLOOD VESSEL GRAFTS. The materials available for arterial grafting are autogenous veins,



Fig. 15-36. Local obstruction in common iliac artery, ideal for endarterectomy.

heterologous arteries, various fabrics, and homologous arteries Arterial heterografts are the least satisfactory substitutes Autogenous veins are preferable to fabric prostheses in peripheral vessels, but vein grafts are not suitable in the aorta or iliac vessels because of possible aneurysm formation, thrombosis, and calcification Synthetic textiles (Orlon, Dacron, nylon, etc) work well in the aorta and the iliac arteries but commonly thrombose in arteries the size of the femoral and popliteal They should only be used, at present, in older patients, or when a homologous preserved artery is not available Thus, homologous freeze-dried arteries are preferable as grafts in all sites. The preparation and storage of these grafts in "banks" is *now routine. The best alternative in peripheral vessels is an autogenous vein, where the site will be supported by the patient's tissues, e g., superficial* femoral artery in Hunter's canal.

Technique of Vascular Anastomosis End-to-end anastomosis of the vessel and the graft is carried out by means of either an everting *mattress or* continuous over-and-over stitch of Nos 00000 *or* 0000 arterial silk or Mersalin The end-to-end technique is necessary in the repair of *major* arteries. *Recently*, the bypass technique has become more *popular*, since it (1) allows a larger anastomosis *to be made* (2) [illegible]

quir [illegible]

of e[illegible]

geon to choose a healthy part *of the vessel wall* for his suture line. The early *optimism, however,* is now receding and the *bypass is not considered to be any more successful, on a long-term basis, than the end-to-end procedure, and it has not widened the indications for direct surgery* In the bypass method, the end of the graft *is sutured* into the side of the artery above and below the obliterated *segment by* means *of* an everting mattress stitch with silk In atherosclerotic vessels, a continuous over-and-*over stitch* is preferable to the everting mattress stitch *and* the needle must always pass from the inside *of the* host artery outward This maintains *apposition* of the intima and media of the atherosclerotic *artery* and prevents lifting up of atheromatous plaques and dissection of the vessel wall

Where fabric is used, the usual arterial *anastomosis* is made but, before the clamps are permanently released, the graft should be allowed to fill with the patient's blood in order that the *interstices of the* textile may fill with fibrin and so excessive bleeding *will be* avoided. Preclotting of the tube using the recipient's blood *may also be* used, if care is taken to express all clot before the final anastomosis is made Fabric is more difficult to sew because it lacks elasticity. Fabric prostheses must also be precisely correct in their length or buckling and thrombosis are likely to occur. However, they do not interfere with blood flow distally and doubtless will be the graft material of the future, when an ideal fabric, biologically inert, strong, flexible, and clot-resistant is available *since* the fabric, as well as a *freeze-dried graft, is primarily a strut. When preserved artery grafts are* used, the elastic fibers remain, but show marked degeneration in later years and the questions of late aneurysm formation, early degeneration, and calcification of the grafts are not yet *completely settled.*

Relief of Intermittent Claudication. The most common complaint in occlusive vascular disease is *pain in the calf on walking (intermittent claudication).* This pain may occur elsewhere, i e , in the buttock, thigh, and foot. In high arterial blocks, claudication may be improved by *sympathectomy but this is not* usual. Relief *of claudication* is usual after a *successful* arterial reconstruction, but relief of pain, alone, should not be the object of direct surgery unless the pain is crippling. There *are still* occasional patients who have good peripheral nutrition and in whom sympathectomy has not relieved intermittent claudication. For them, disabling claudication *can be relieved* or improved by inactivation of the muscles of the *painful calf,* almost always the gastrocnemius. *The* procedures—gastrocnemius *neurectomy* and tendo achillis *tenotomy*—are purely palliative and have no effect on the *peripheral* circulation or nutrition.

NEURECTOMY Gastrocnemius neurectomy is performed through a *short vertical* incision beginning at the crease behind the knee joint over the popliteal fossa and *extending* distally 10 cm The fascia is split, the *short* saphenous vein is retracted, and the muscular *branches to* the two heads of the gastrocnemius *identified and* confirmed by stimulation An inch *or so of each* nerve is resected and the incision closed in layers. There is no need to denervate *the* soleus as *it rarely* causes claudication. The foot and calf of the *leg* are supported postoperatively by an elastic bandage *to* prevent thrombosis in the vein of the inactivated *muscle* Castrocnemius neurectomy weakens the calf but it enables the patient to walk five *or* ten times far*ther than* before and is of great value in the aged, incapacitated *patient* with good *peripheral* nutrition.

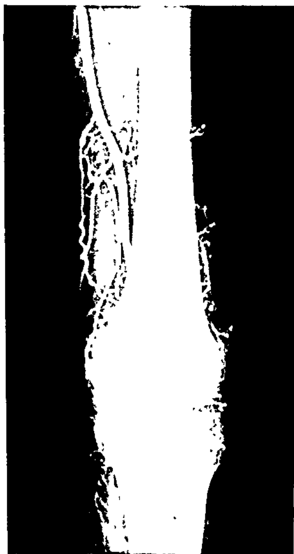


Fig. 15-35. Wasp-waist constriction of popliteal artery, free from atheroma and ideal for endarterectomy.

Better results are obtained in the iliac vessels, but here grafts are preferable except in the case of local obstructions (Fig 15-36)

Technique. The principle of thromboendarterectomy is to remove the obliterated segment through a plane of cleavage in the media Thus the atheromatous plaques and thrombus are removed along with the intima and media out to but not including the external elastic lamina The adventitia and the outer layer of the media remain as the vessel wall. Although the remaining artery wall is attenuated it is capable of withstanding the arterial blood pressure without aneurysm formation. Long-term anticoagulant therapy, for years if necessary, will ensure that recurrent thrombosis is rare

The artery is exposed through a long skin incision overlying the thrombosed segment A longitudinal incision is made into the vessel wall after establishment of proximal and distal control of the patent portions of the vessel by means of bulldog clamps. Careful blunt dissection with a MacDonald dissector will develop a plane of cleavage in the media. The thrombus can then be easily stripped up and down the vessel. Bleeding from collaterals is controlled by means of small bulldog clamps Once the offending thrombus is removed, the intima of the proximal and distal portions of the vessel must be stitched to the vessel wall in order to prevent dissection and thrombosis. The vessel wall is carefully sutured with No. 00000 arterial silk and the clamps are removed. Multiple short incisions may be made, rather than a single long one, and special strippers may be used to mobilize the thrombus, but when this is done there is an implication that too long a segment is being disobliterated. The incision is closed without drainage and heparin is started 6 hours postoperatively. Long-term anticoagulant therapy is commenced the next day with a Dicumarol derivative and is continued for months or years to minimize recurrent thrombosis.

BLOOD VESSEL GRAFTS. The materials available for arterial grafting are autogenous veins,



Fig. 15-36. Local obstruction in common iliac artery; ideal for endarterectomy.

Below-knee When a transmetatarsal amputation has failed, or if gangrene involves the heel or dorsum of the foot, or if uncontrollable infection of the foot or tendon sheaths is present, the only problem is whether or not the stump of an amputation below the knee will heal The knee joint should be preserved at all costs, particularly if the other leg may be lost, as it greatly assists the patient to get in and out of bed and to change position, and favors rehabilitation and the management of a prosthesis Arteriography may help the decision, as it may show collateral vessels going below the knee when the popliteal pulse cannot be felt. Sometimes, the final decision is deferred until the time of operation when the amount of bleeding on incising the muscles will aid the surgeon in deciding upon the ultimate viability of the flaps. Better control of infection, more frequent use of simultaneous sympathectomy, and better techniques, make this amputation the one of choice

With the patient under general anesthesia, without using a tourniquet, and as gently as possible, equal flaps are raised to leave a 5-in tibial stump. The muscles and tibia are sawed through at this level and the fibula is divided 1 in. proximally. The subcutaneous crest of the tibia is beveled, all vessels are caught and tied, and the nerves are separately divided after they have been pulled downward and then allowed to retract. A soft corrugated drain is left in and the skin edges approximated with interrupted silk sutures A firm pressure dressing is applied The drain is removed after 48 hr and the patient is allowed to ambulate on crutches and commence physical therapy on the third day This procedure improves morale and ensures that flexion contracture will not occur.

Above-knee When gangrene or infection extends too high to permit the fashioning of adequate below-knee flaps, when the blood supply below the knee is inadequate, and when a below-knee amputation fails, then an operation at a higher level is necessary. An above-knee amputation is usual when the femoral artery is not palpable and also when gangrene follows an acute embolism or thrombosis because adequate collateral circulation has not had time to develop.

The same general principles as outlined for a below-knee amputation hold. The anterior flap raised is slightly longer than the posterior flap, and the femur is transected to leave a 10- to 12-in stump The deep fascia is raised, with the skin and the muscles divided at the same level as the bone All bleeding points are meticulously controlled The sciatic nerve should be ligated with catgut, as it usually contains a large collateral vessel The muscles are approximated over the end of the bone, the flaps of deep fascia are apposed and the skin is gently closed with interrupted silk sutures after a through-and-through corrugated drain has been inserted between fascia and muscle A pressure bandage is applied The drain is removed after 48 hr Again, early ambulation and physical therapy are encouraged, and a pylon for walking is applied within a few weeks so that the patient does not lose his morale and his balancing powers.

The *Stokes-Gritti* amputation is one that every surgeon should keep in mind as it is especially applicable to the elderly patient in poor general condition It can be performed in 15 min. with almost no blood loss, since only skin is cut. A curved incision beginning at the adductor tubercle crosses the tibia at its tubercle and incorporates the patella in this flap A transverse posterior incision joins the opposite end of the first incision over the outer condyle of the femur. The leg is disarticulated through the knee and the major vessels caught in the popliteal fossa The femur is sawed through at the level of the adductor tubercle and the joint surface of the patella is sawed off and sewed to the

Amputations of the upper extremities are seldom needed in occlusive vascular disease and then usually in thromboangiitis obliterans They need no special consideration here but are managed along the same general principles as those followed for lower-limb amputations.



Fig. 15-37. Healed amputation sites of two toes removed for diabetic gangrene.

TENOTOMY. Although tenotomy of the Achilles tendon is advocated in some clinics, the author does not recommend it, since it is disabling and a patient who has undergone bilateral tenotomy needs a cane to maintain his balance.

While the patient is under general anesthesia, the tendon is divided by inserting a tenotomy knife into the medial side of the ankle just above the insertion of the tendon into the os calcis. There is no bleeding and the skin need not be sutured. The patient walks the next day, and can walk slowly (or perhaps better shuffle) for long distances without pain. If both sides are treated they should be tenotomized at an interval of several months. There is a tendency to reconstitution of the tendon with fibrous tissue but usually without recurrence of claudication. The procedure often cripples the patient, who then needs a cane to maintain his balance and must assume a shuffling gait. Tenotomy should never be performed in the presence of severe ischemia, as infection severe enough to necessitate amputation may ensue, and has been seen by the author.

AMPUTATION. When the blood supply to a limb fails, death of tissue results. Whether this *gangrene* is "wet" or "dry," removal of the dead tissue is necessary. The onset of gangrene may be delayed by medical measures and by encouraging the collateral circulation through sympathectomy. Occasionally, amputation is necessary even in the absence of overt gangrene, because of spreading infection, severe rest pain, or ischemic neuritis. Amputations should be as conservative as possible —that is, as low as is compatible with healing by first intention but as high as necessary to provide a functional stump. This is most important in the elderly patient, not only for psychological and mechanical reasons, but also because, the higher the level of amputation, the higher the mortality rate. Local anesthesia and tourniquets must never be used and tissues must be handled gently.

The techniques of the amputations are standard and will be discussed but briefly. Four levels of amputation are in general use in treating occlusive vascular diseases: digital (usually toes), transmetatarsal, below-knee, and low-thigh.

Digital. When gangrene is localized, well demarcated, and not spreading, then one or even two toes may be safely removed (Fig. 15-37). General anesthesia is used and a circular incision is made around the base of the toe, which is disarticulated at the metatarsophalangeal joint. The cartilage of the metatarsal head should be nipped away with a rongeur, otherwise sequestration may occur. The skin is loosely apposed with one or two interrupted silk or wire stitches. In diabetics, where infection may have spread to the tendon sheath and perhaps even caused osteomyelitis of the metatarsal bone, the affected toe and its metatarsal are removed, and a long plantar incision is used to ensure adequate drainage. Again, the tissues are loosely approximated or they may even be packed loosely with petrolatum gauze and allowed to heal by second intention under adequate antibiotic cover and diabetic control. If there is any doubt about the healing, local amputation is combined with sympathectomy.

Transmetatarsal. When several toes are gangrenous, amputation through the foot is preferable. Again, if the gangrene is well-demarcated to the toes, with no (or minimal) extension to the foot and controlled infection, the best results will be obtained. The presence of at least one pulse at the ankle will ensure success. Lumbar sympathectomy performed simultaneously will increase the number of successful results. The author had most success with this procedure in younger diabetics and in cases of gangrene which followed acute arterial occlusion. A long plantar flap and a transverse dorsal flap are used. The latter is not undermined but carried down to the metatarsal bones, which are divided individually proximal to their heads by means of a Gigli saw. The tissues are handled gently and careful hemostasis permits the surgeon to close the wound with interrupted silk stitches, without drainage and without tension. Little is lost by attempting this procedure since it is the only major amputation after which an amputee can walk without crutches or a prosthesis.

Below-knee. When a transmetatarsal amputation has failed, or if gangrene involves the heel or dorsum of the foot, or if uncontrollable infection of the foot or tendon sheaths is present, the only problem is whether or not the stump of an amputation below the knee will heal. The knee joint should be preserved at all costs, particularly if the other leg may be lost, as it greatly assists the patient to get in and out of bed and to change position, and favors rehabilitation and the management of a prosthesis. Arteriography may help the decision, as it may show collateral vessels going below the knee when the popliteal pulse cannot be felt Sometimes, the final decision is deferred until the time of operation when the amount of bleeding on incising the muscles will aid the surgeon in deciding upon the ultimate viability of the flaps. Better control of infection, more frequent use of simultaneous sympathectomy, and better techniques, make this amputation the one of choice

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14

Physiology of systemic arteriovenous fistulas

HARRY A. BLISS

The establishment of a large communication between a systemic artery and vein results in a number of complex reactions on the part of the organism Modern research in this area began after World War I, when gunshot wounds produced arteriovenous fistulas in many soldiers. The work of Matas, Lewis and Drury, Reid, Holman (1937), and others emerged from this era Traumatic fistulas from World War II and the Korean conflict provided further impetus to research

Results of this work have not only afforded insight into the circulatory changes due to arteriovenous fistulas, but have also provided data on the control of cardiac output, blood volume, and renal excretion of salt and water The subject will be discussed first in terms of the acute adjustments to opening or closing a fistula, and, second, in terms of the changes resulting from more long-standing lesions and their surgical eradication.

ACUTE ADJUSTMENTS TO AN ARTERIOVENOUS FISTULA

Opening a large fistula between a systemic artery and vein creates an avenue of lower resistance through which arterial blood readily passes. A portion of this blood proceeds distally to perfuse the limb, but *the larger part seeks the low resistance of the proximal vein and thus quickly returns to the heart* The quantity of blood taking this short circuit back to the heart is determined by the cardiac output and by the inflow resistance of (1) the artery itself, (2) the fistula, (3) the vasculature peripheral to it, and (4) the proximal vein and its central connections These parameters are influenced by (1) the ability of the heart to increase its output, (2) blood viscosity, (3) arterial distensibility, (4) the size and shape of the fistula, (5) venous tone and volume, and (6) the resistance to filling of the right heart. These factors and the measurable quantities reflecting them are discussed below.

Arterial Blood Pressure. When an arteriovenous fistula is suddenly opened, systolic, diastolic, and mean blood pressures drop significantly during the first two beats. After this, pressures tend to return toward normal. Diastolic pressure often recovers less than systolic pressure, so that the pulse pressure may widen Mean pressure, recorded over a period of minutes after fistula opening, shows no change or fall, and occasionally it may actually rise The factors related to these changes in mean blood pressure are discussed below.

HEART RATE. The sudden fall in heart rate upon manual occlusion of arterial inflow to an arteriovenous fistula was first noted by Nicoladoni and Branham This observation has subsequently been confirmed by many workers, both in human beings and in animals. Matas noted that the Nicoladoni-Branham sign may disappear when congestive failure occurs Atropine usually prevents the fall in heart rate without materially changing the blood pressure rise, which invariably occurs It has therefore been postulated that a *vagal reflex*, mod-

erated through the effect of the elevated blood pressure on the aortic and carotid sinus pressoreceptors, causes the bradycardia

The sudden formation of an arteriovenous fistula may cause a rise in the heart rate in animals given the lesion acutely, but this change is not invariable. The latter fact, plus the possibility of a *Bainbridge reflex* causing tachycardia through an increase in right atrial filling, led Coleridge and Linden to reevaluate the mechanism of this phenomenon in dogs.

Keeping the mean blood pressure constant by means of small arterial transfusions during a gradual opening of the fistula, these investigators found that heart rate rose nonetheless. Reasoning that increased pulse pressure might be instrumental in increasing pressoreceptor activity, they occluded the carotid arteries proximal to the carotid sinus Heart rate still increased in half of the animals when the fistula was opened. Although right atrial pressure always rose immediately upon fistula opening, it frequently fell to control levels over a period of minutes, although the elevated heart rate persisted. Curiously, the heart rate response to opening the fistula was abolished when the control heart rate was sufficiently rapid to prevent the occurrence of sinus arrhythmia. Coleridge and Linden concluded that the mechanism of increased heart rate on opening an arteriovenous fistula remained unknown, but that increased venous return, by reducing vagal tone in an unknown way, might be, at least partially, responsible.

THE HEART, CARDIAC OUTPUT, AND BLOOD VOLUME. An immediate rise in cardiac output following the opening of an arteriovenous fistula has been frequently observed The ratio of the short-circuit flow through the fistula to the increase in cardiac output bears an obvious relation to the adequacy of the circulation in general and to the work of the heart in particular.

Frank and his coworkers investigated the determinants of this ratio in an ingenious dog preparation in which short-circuit (shunt) flow could be altered at will They found that the amount of increase in cardiac output was a function of the shunt flow [illegible]
outp[illegible]
sever[illegible]
20 per cent of the control cardiac output, flow through the fistula was equal to the increase in cardiac output [illegible]
peripheral [illegible]
therefore [illegible]

shunt flow was more than 27 per cent of the control cardiac output, however, cardiac output increased by less than the amount of the shunt flow. This reduction in blood flow to the remainder of the body (body flow) resulted in vasoconstriction, elevating systemic peripheral resistance in all animals In those with less severe shunts, this vasoconstriction was sufficient to maintain mean arterial blood pressure at the control level With larger fistulas, however, blood pressure fell despite vasoconstriction.

In the last-mentioned group of animals, 100 ml of isotonic saline solution was administered intravenously while the fistula remained open. A large rise in cardiac output, mainly directed into increasing body flow, ensued. Systemic peripheral resistance fell sharply and mean blood pressure reached control levels. The increase in cardiac output above control was now equal to the shunt flow. In one animal, a continuous infusion of 100 ml of saline solution over a 10-min period allowed a shunt flow equal to 77 per cent of the control cardiac output to be attained as well as a similar percentage increase in cardiac output, so that blood pressure and systemic peripheral resistance were maintained at constant levels.

These experiments appear to demonstrate that, *with small arteriovenous fistulas*, the increase in cardiac output can equal the shunt flow and systemic vasoconstriction, at least on the arterial side of the circulation Cardiac output probably increases, partly through increased ventricular emptying, and partly through mechanisms tending to force venous blood toward the heart These mechanisms may consist of system c venoconstriction or an increased venous volume, although the origin of the latter is unclear

With larger fistulas, these workers conclude that there is a pressure gradient between the fistula and the heart, insufficient to maintain the ratio of 1 between the increase in cardiac output and shunt flow In their view, it is inadequacy of venous return, occasioned by inability to maintain the requisite heartward venous rate of flow, that is primarily responsible for the reduction in body blood flow

Whatever the mechanism involved, it is apparent that, in arteriovenous fistulas, an increase in blood volume makes an important contribution to maintaining blood pressure and flow to the rest of the body.

As Frank et al. point out, there is little evidence that the failure to maintain body flow

simultaneously with large shunt flows is due to the inability of the heart to meet the increased load placed upon it. Even in the group of animals with the largest fistula flows, the increase in central venous pressure was small, averaging 8 mm H_2O. Other workers also found very little or no rise in right atrial pressure after acutely opening an arteriovenous fistula. Indeed, the heart becomes smaller for the first few hours after establishment of the fistula, despite the undoubted increase in cardiac work noted in the early investigation of Gley and Gomez, which were confirmed more recently.

Pulmonary arterial and left atrial pressure show a slight but definite rise when a fistula is acutely opened Probably this has the same significance as the slight rise in right atrial pressure

Renal Function. Hilton et al. found an immediate decrease in renal plasma flow and rate of sodium excretion in each of 10 dogs with an acute arteriovenous fistula. Nine of ten animals showed reduction in urine flow and in glomerular filtration rate. Filtration fraction rose in all dogs, presumably as a result of efferent arteriolar constriction. These observations suggest a possible mechanism for the salt and water retention seen in patients with chronic arteriovenous fistula This retention contributes to the increased blood volume which helps compensate for the altered hemodynamics in these individuals

Local Hemodynamics. The formation of an arteriovenous fistula sufficiently large to be visible by angiography always produces a characteristic continuous murmur and thrill, according to Edwards and Levine, who have described the characteristics of this murmur in detail. Presumably the murmur is produced by turbulent blood flow through the fistula It can be obliterated by occlusion of either the proximal artery or vein

The pressure/flow relationships in the two arterial and two venous tributaries of the fistula are highly variable They depend on the cardiac output and on the resistance factors previously mentioned If the fistula is large, or if the cardiac output is for any other reason inadequate to provide normal body flow, vasoconstriction in the limb bearing the fistula will further decrease blood flow distal to the shunt This effect sets the stage for the pallor, coolness, and occasional gangrene of extremities the blood supply of which is acutely compromised by a sizable arteriovenous fistula. The great elevation of distal venous pressure produces prompt and obvious edema

Schenk et al. have recorded pressure and flow in the four limbs of acutely established femoral and carotid arteriovenous fistulas in dogs. They found that inflow to the distal extremity passes through the distal vein rather than the artery. Holman and Taylor noted similar effects, and added the information that, with larger fistulas, flow in the distal artery is definitely *toward the fistula* Furthermore, they noted that ligation of the proximal vein results in extreme swelling of the extremity. No swelling occurs when the distal vein alone is tied off. Distal artery ligation prevents development of the extensive collateral circulation discussed below.

CHRONIC ADJUSTMENTS TO AN ARTERIOVENOUS FISTULA

The hemodynamics of a chronic arteriovenous fistula differ from those of the acute lesion because of the gradual occurrence of several important effects. These primarily relate to the heart, the blood volume, the kidney, and the local circulation distal to the fistula.

The Heart, Cardiac Output, and Blood Volume. Many observers have substantiated the presence of increased cardiac output in patients and animals with chronic arteriovenous fistula. This elevation is reduced, but generally not eliminated, on manual occlusion of the proximal artery or vein or when the surgeon eradicates the fistula. Many days may elapse after surgery before cardiac output returns to normal levels.

Similarly, most investigators, using serum-albumin-tagging dyes, have found an increase in plasma volume, and, indirectly, in blood volume in nearly all individuals with chronic arteriovenous fistula. Epstein et al (1955), using P^{32}-tagged red blood cells, found no increase in total red-cell mass in dogs 2 to 6 weeks after the creation of an aorta–vena cava shunt A large increase in Evans blue volume occurred in all animals.

These findings indicate that the increase in blood volume occurs through a rise in plasma volume only. The work of Lillehei et al., dem-

onstrating a rise in thiocyanate ("extracellular fluid volume") space in dogs with chronic arteriovenous fistulas, lends support to this conclusion. Furthermore, both the latter authors and Holman found a gradually falling hemoglobin concentration and hematocrit reading in such preparations.

After surgical correction of the arteriovenous communication, the plasma volume gradually falls but, like cardiac output, may require days to attain normal levels.

After the early decrease in heart size, when an arteriovenous fistula is established, *the heart gradually dilates and hypertrophies* The degree of enlargement probably depends on the degree of increase in blood volume, cardiac output, and cardiac work, and on the ability of the heart to meet this increased demand.

Right and left atrial pressures, left ventricular end-diastolic pressure, and pulmonary arterial pressures rise, even in the absence of apparent cardiac failure Heart rate remains elevated Arterial diastolic pressure is usually less than normal, although mean pressure is not greatly affected. On manual occlusion of the artery leading to the fistula, or when the latter is surgically eradicated, all these pressures move in the direction of normal, except mean arterial pressure, which rises above normal The heart shadow may increase in size for 24 hr at this time It then gradually becomes smaller over a period of days to weeks

Heart Failure. Among the earliest reports of progressive congestive heart failure secondary to arteriovenous fistula are those of Stewart and of Sir William Osler. This clinical situation is now well recognized and is often classified in the syndrome of "high-output" congestive failure, along with the heart failure seen in anemia, beriberi, and certain other diseases Dyspnea, pulmonary edema, ascites, peripheral edema, and hepatomegaly may all occur

Matas found evidence of severe chronic myocardial insufficiency in approximately half of his 31 patients with arteriovenous fistulas, many of long duration On the other hand, death from cardiac failure has been reported as early as 4 days after occurrence of the injury causing the fistula As one might suspect, patients with very large shunts who are seen early may suffer from symptoms more suggestive of shock than of congestive heart failure Presumably inadequate compensatory blood-volume adjustment and low body blood flow play major roles in producing this situation

In general, congestive failure is more likely to occur in (1) older patients with long-standing arteriovenous fistulas; (2) individuals with other types of heart disease; and (3) those with large shunts located close to the heart Surgical elimination of the fistula promptly relieves the symptoms of heart failure and results in complete cure

Since plasma volume and interstitial-fluid volume increase in nearly all patients with chronic arteriovenous shunts without congestive heart failure, one may inquire whether inadequate myocardial performance forms the basis for the larger increases in these distribution volumes in patients with arteriovenous fistula and gross edema The answer to this question is not entirely clear. Evidence exists, however, that edematous patients and animals with arteriovenous fistulas have reached the upper limit of the heart's pumping capabilities. After producing aorta–vena cava fistulas, Epstein and Ferguson found many dogs showed rales, weakness, and ascites over a period of several months. When these animals were given blood or saline-solution infusions, cardiac output and work either fell or showed inadequate rises, despite elevation of left ventricular end-diastolic pressure Therapeutic doses of lanatoside C did not affect these abnormalities These apparently maximum levels of cardiac output and work were not significantly different from the maximum levels observed in normal dogs similarly infused.

Campbell reported similar findings in acutely exercised patients with arteriovenous fistulas Patients without congestive heart failure were able to increase cardiac output under stress, but those with this syndrome showed a decrease in cardiac output during exercise.

These responses, in addition to the renal-function abnormalities cited below, are remarkably similar in patients with "high-output" and with "low-output" cardiac failure. This lack of fundamental difference between the two groups suggests that the level of cardiac output is less important than its inadequacy to fill the arterial bed and provide normal organ perfusion, especially in the kidney. Consequent

abnormal renal sodium and water retention, probably aggravated by increased *aldosterone* excretion, result in the edema seen in these patients.

Thus, in any sizable arteriovenous fistula, increases in cardiac output and plasma volume together maintain body blood flow. When the maximum cardiac output has been achieved, further increases in plasma volume occur, with sufficient sodium and water retention to cause edema. The syndrome of congestive heart failure in these patients may, therefore, be thought of as an extension of the normal adaptive response.

Renal Function. In patients with arteriovenous fistula without congestive heart failure, Epstein (1953) found normal renal hemodynamics. When the inflow artery to the fistula was manually occluded for 20 to 50 min, a significant increase in sodium excretion occurred without change in renal plasma flow. No change in sodium excretion took place when the artery was similarly occluded after surgical eradication of the fistula. Epstein concludes that a regulatory mechanism, sensitive to the degree of arterial filling caused the observed rise in sodium excretion This mechanism may be, at least partly, responsible for decreased sodium excretion in patients with arteriovenous fistula and other diseases

Local Hemodynamics. If the arterial and venous tributaries of an arteriovenous fistula are surgically closed within days or weeks after the causative trauma, gangrene of the limb may ensue. Blood flow in an extremity bearing such a fistula is distinctly subnormal in this early period.

During the months and years following establishment of the fistula, however, an extensive distal collateral circulation develops. Lewis (1940) found with each passing year that the involved extremity became warmer and blood flow distal to the fistula increased until it became larger in the involved extremity than in the opposite normal one The limb hypertrophies and remarkably large superficial and deep venous channels often develop Four-point ligation of the fistula may be performed with impunity when collaterals have developed.

Lewis believed that collateral-circulation development occurred in response to ischemia distal to the fistula. Holman (1952) vigorously opposed this conclusion. He constructed femoral arteriovenous fistulas in dogs with thigh amputations in the extremity bearing the fistula. The distal artery was ligated except for a few small branches. Nonetheless a large collateral circulation developed, far beyond the needs of the tissues. In both patients and animals with large arteriovenous fistulas distal-artery blood flow is in the direction of the fistula by the time collaterals have developed. If both the proximal artery and vein are clamped at this time, distal arterial pressure is approximately systemic, a finding demonstrating sizable communications between the latter vessel and other arteries Holman concludes that collateral development depends on the relative size of the fistula and the proximal artery. When the fistula is large, collaterals develop because blood from branches of other arteries distal to the fistula seeks the low resistance outlet of the fistula through their anastomotic connections with the distal artery Prior to adequate collateral development, the limb thus depends on blood flow through the distal vein for its nutrition. By eliminating this channel, early four-point ligation of the aneurysm jeopardizes viability of the extremity. Evidence of collateral circulation should therefore be present before surgery is undertaken.

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Circulation time in arteriovenous fistula

WILLIAM M. HITZIG

In arteriovenous fistula, pronounced systemic circulatory effects are produced; their intensity depends upon the size of the fistula and its proximity to the heart. As a consequence of the shunt, *circulating* blood volume is increased, and the increased venous return becomes translated into an augmented cardiac output. Through the medium of compensating peripheral mechanisms, in which vasodilatation plays a dominant role, blood flow may accelerate to aid in establishing a balance between an increased venous return and an increased cardiac output. The circulation time may remain *normal* or may be disproportionately *reduced*. Such reduction occurs only in the early stage of overcompensation before myocardial fatigue and heart failure appear. When, in arteriovenous fistula, progressive failure of the circulation develops, the circulation time reveals either retardation of blood flow or relative acceleration. In the decompensated stage of arteriovenous fistula, it is not unusual to find a circulation time still within the upper limits of normal. Apparently cardiac output, although it is diminished, is still higher than normal

abnormal renal sodium and water retention, probably aggravated by increased *aldosterone* excretion, result in the edema seen in these patients.

Thus, in any sizable arteriovenous fistula, increases in cardiac output and plasma volume together maintain body blood flow. When the maximum cardiac output has been achieved, further increases in plasma volume occur, with sufficient sodium and water retention to cause edema. The syndrome of congestive heart failure in these patients may, therefore, be thought of as an extension of the normal adaptive response.

Renal Function. In patients with arteriovenous fistula without congestive heart failure, Epstein (1953) found normal renal hemodynamics. When the inflow artery to the fistula was manually occluded for 20 to 50 min, a significant increase in sodium excretion occurred without change in renal plasma flow. No change in sodium excretion took place when the artery was similarly occluded after surgical eradication of the fistula. Epstein concludes that a regulatory mechanism, sensitive to the degree of arterial filling caused the observed rise in sodium excretion. This mechanism may be, at least partly, responsible for decreased sodium excretion in patients with arteriovenous fistula and other diseases

Local Hemodynamics. If the arterial and venous tributaries of an arteriovenous fistula are surgically closed within days or weeks after the causative trauma, gangrene of the limb may ensue. Blood flow in an extremity bearing such a fistula is distinctly subnormal in this early period

During the months and years following establishment of the fistula, however, an extensive distal collateral circulation develops Lewis (1940) found with each passing year that the involved extremity became warmer and blood flow distal to the fistula increased until it became larger in the involved extremity than in the opposite normal one. The limb hypertrophies and remarkably large superficial and deep venous channels often develop. Four-point ligation of the fistula may be performed with impunity when collaterals have developed

Lewis believed that collateral-circulation development occurred in response to ischemia distal to the fistula. Holman (1952) vigorously opposed this conclusion. He constructed femoral arteriovenous fistulas in dogs with thigh amputations in the extremity bearing the fistula. The distal artery was ligated except for a few small branches. Nonetheless, a large collateral circulation developed, far beyond the needs of the tissues. In both patients and animals with large arteriovenous fistulas, distal-artery blood flow is in the direction of the fistula by the time collaterals have developed. If both the proximal artery and vein are clamped at this time, distal arterial pressure is approximately systemic, a finding demonstrating sizable communications between the latter vessel and other arteries. Holman concludes that collateral development depends on the relative size of the fistula and the proximal artery. When the fistula is large, collaterals develop because blood from branches of other arteries distal to the fistula seeks the low resistance outlet of the fistula through their anastomotic connections with the distal artery. Prior to adequate collateral development, the limb thus depends on blood flow through the distal vein for its nutrition. By eliminating this channel, early four-point ligation of the aneurysm jeopardizes viability of the extremity. Evidence of collateral circulation should therefore be present before surgery is undertaken

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I

Clinical picture and treatment of systemic arteriovenous fistulas

LEO M. ZIMMERMAN

As an outgrowth of the rapid expansion of surgery of the heart and arterial system, shunts between the right and left circulations are playing an increasingly important part in the diagnosis and management of cardiovascular malformations and diseases The first form of vascular shunt to be recognized, and the one most intensively studied, is *acquired arteriovenous fistula* This abnormal communication was first described by William Hunter (1757), whose case resulted from a simultaneous penetration of a vein and artery during the act of blood letting

Five years later, Hunter found a second case of similar origin, and made this perceptive commentary on the pathogenesis and manifestations of the condition

> In a former paper upon the Aneurysm, I took notice of a *species* of that complaint, which so far as I know, had not been mentioned by any author, viz where there is an *Anastomosis* or immediate communication between the artery and vein at the part where the patient had been let blood, in consequence of the artery being wounded through the trunk of the vein, so that blood passes from the trunk of the artery into the trunk of the vein, and so back to the heart
>
> ° ° °
>
> It will differ in its symptoms from the common spurious Aneurysm principally thus The vein will become dilated or become varicose, and it will have a pulsatile jarring motion, on account of the stream from the artery It will make a hissing noise, which will be found to correspond with the pulse, for the same reason The blood of the tumor will be altogether, or almost entirely fluid, because kept in constant motion. The artery, I apprehend, will become larger in the arm, and smaller at the wrist, than it was in the natural state, which will be found out by comparing the size and the pulse of the artery in both arms at these different places. The reason of which I will speak of later . . And the dilatation of the veins may also vary on account of the size of the artery that is wounded, and of the size of the orifice in the artery, and in the vein

Since this initial and graphic description, this form of arteriovenous shunt has been extensively investigated by numerous workers here and abroad. Of the many who have contributed to an understanding of the altered physiology in arteriovenous fistula, E Holman should be given particular mention. During the greater part of his scientific and surgical career, he has devoted himself to the study of the surgical physiology of this lesion More than any other person he has carried the problem to the experimental surgery laboratory Much of our knowledge of the circulatory effects of arteriovenous fistula in particular, and of cardiovascular shunts in general, has come from the animal studies of Holman More recent investigators have confirmed, amplified, and quantitated his findings with refined investigative methods

Arteriovenous fistula is an abnormal communication between an artery and a vein Such abnormal communications may be congenital or acquired, only the acquired forms will be

considered here. These are usually of traumatic origin, surgical or otherwise, although spontaneous fistulas occasionally develop as a result of vascular disease, including syphilis, atherosclerosis, or embolic infections Most of the traumatic fistulas occur in the extremities, although they may be found in the visceral vessels and in the great vessels of the chest or neck. Penetrating injuries, particularly gunshot or stab wounds, are commonly the cause of fistulas, and the high-velocity missile wounds of modern warfare have furnished an ample number of such lesions for study in recent decades.

REGIONAL HEMODYNAMICS

Dilatation of the arterial and venous trunks proximal to an arteriovenous fistula was observed by Hunter and studied in detail by Holman The work of Schenk et al revealed that the forward flow was markedly increased in the artery proximal to the shunt. In the proximal vein, the forward flow was similarly augmented, and had taken on a pulsatile character *The distal artery*, on the contrary, *showed* a to-and-fro flow of equal volume, with an absence of mean arterial flow. In the distal vein, *the flow was reversed*, away from the heart Pressure relations in these experiments were as follows In the proximal artery the mean pressure dropped slightly (from 160 to 150 mm Hg) and the pulse pressure somewhat decreased. The distal artery showed a marked reduction in diastolic, systolic, and mean pressures Pressures in *the proximal vein* varied according to the proximity to the fistula, the augmented pressure *from the arterial limb* becoming rapidly lost in the distensible venous bed The pressure in the distal vein equaled that in the distal artery

The absence of consistent hypertension in the preatrial portions of the venae cavae and in the atria themselves has been discussed. In addition to the distensibility of *the proximal* venous bed, the reduced diastolic filling pressure of the right ventricle enables it to receive large volumes of blood without sustaining tricuspid insufficiency and atrial hypertension

The local circulation of the extremity which harbors an arteriovenous fistula reflects the above-described flow and pressure changes. The fistulous opening competes with the capillary bed for the available blood brought to the part by the proximal artery. The relative adequacy of the distal circulation is determined by the volume deflected, and this, in turn, by the size of the opening

Pauporte and his coworkers studied the blood turnover rates in the thigh and the tibia by means of a *radioactive dye* (I^{131} *rose* bengal) and an external gamma-ray detection system, in animals with femoral arteriovenous fistulas. The values in the thigh were inconclusive because of the to-and-fro flow, as was described above. In the tibia, however, the blood turnover rate was reduced, and the degree of reduction was proportional to the size of the fistula With the passage of time, the flow tended to return to normal This tendency toward spontaneous improvement was noted by Holman and others, and is presumably affected by an increasing collateral circulation The phenomena attendant upon collateral vasculature will be commented upon later.

The venous trunk, receiving the blood flow through the fistula under arterial pressure, becomes dilated both proximally and distally. Stretching of the lumen of the veins beyond the closing capacity of the valves leads to *valvular incompetence* and *formation of varicose veins*. The sequelae of venous insufficiency, edema, and dermatosis are likely to develop.

EFFECTS OF COMPRESSION OR CLOSURE OF THE FISTULA

Compression of an arteriovenous fistula instantly stops the flow of blood through the parasitic circuit, and the physiologic alterations are reversed William Hunter, in his original description of this condition, noticed that *compression of the fistula* or of the proximal *artery abolished* the thrill and bruit. Nicoladoni (1875), while recording a pulse tracing in the presence of an arteriovenous fistula, observed *an abrupt slowing* of the heart rate when the fistula was occluded by digital compression.

Fifteen years later (1890), Branham made *the* following statement:

> The most mysterious *phenomenon* connected with this case (of an arteriovenous *fistula*), one which I have not been able *to* explain myself or to obtain a satisfactory reason for from others, was slowing of the heart's beat when compression of the ... the wound caused the *heart's*

beat to fall from 80 to 35 or 40 per minute, so to remain until the pressure was relieved Compression of the sound limb produced no such effect Attending the slowing of the heart was a slight dizziness and some dyspnea Examination of the heart showed it to be free from valvular trouble.

This bradycardia, known now as *the Nicoladoni-Branham sign*, or more familiarly as the Branham sign, is pathognomonic of arteriovenous fistula. Slowing of the pulse is accompanied by an elevation of the systolic and diastolic arterial pressures resulting from the elimination of the low peripheral resistance through the shunt The mechanism involved, whereby elevation of the arterial pressure causes slowing of the heart beat (Marey's law), is a vagal reflex originating in pressure-sensitive end organs in the carotid sinus and aortic arch Because this is a vagal effect, it can be abolished by atropine administration. Further alterations in systemic circulatory function occurring after closure of a fistula include reduction in cardiac output and stroke volume The latter is not blocked by atropine (Nickerson et al., 1951b)

Permanent correction of an arteriovenous shunt restores all the circulatory phenomena to normal The blood volume falls, through hemoconcentration and diuresis, within a 24-hr period There is a rapid decrease in heart size and restoration of compensation, provided there are no other cardiovascular abnormalities Only the arterial dilatation persists in long-standing cases, and a late development of aneurysms of the proximal artery has been observed.

COURSE

The natural history of the arteriovenous fistula is determined by the degree of dilatation of the proximal vessels and heart, including the size of the abnormal orifice A vicious cycle becomes established The demand for more blood to "satisfy the appetite" of the fistula leads to the development of collateral vessels which, by augmenting the volume passing through the fistula, tend to further dilate it. This leads to increasing cardiac failure, unless the fistula is surgically closed, until death ensues. One adventitious circumstance, emphasized by Holman, is the restriction of dilatation of the fistula by the formation of cicatricial fibrous tissue. Thus the amount of inflammation may determine the course of changes induced by the fistula.

The development of collateral circulation in the presence of an arteriovenous fistula has been studied in detail by Holman He reported that a richer collateral network is found in the presence of fistulas than in simple arterial aneurysms, or following ligation of an arterial trunk. The reason for this excessive collateral development, chiefly arising *distal* to the fistula, is the low-pressure outflow tract provided by the arteriovenous stoma, which draws blood toward it. Thus, under appropriate conditions, the blood distal to the opening will flow cephalad instead of caudad. Banding or ligation of the artery distal to the fistula prevents the development of the collateral vessels.

Blood Volume and Composition. Increase in the circulating blood volume following the establishment of an arteriovenous fistula has been an accepted phenomenon since it was first reported by Holman (1924). The augmented volume was explained by an initial hemodilution with extracellular fluid, followed by mobilization of the cellular elements from depots in the spleen and liver. The magnitude of the hypervolemia was proportional to the volume of the fistulous diversion of blood A study by Warren et al in a series of patients before and after closure of an arteriovenous fistula showed a significant variation in 44 per cent of the cases and a moderate variation in 56 per cent In general, the elevated volumes were associated with the larger fistulas Investigations by Epstein and Ferguson and others have indicated that the volume increase is largely due to an expanded plasma volume, with little or no change in the total red cell volume The oxygen tension of the venous blood at the fistula site is elevated, approaching that on the arterial side

DIAGNOSIS

The physiologic disturbances incident to a traumatic shunt between an arterial trunk and its accompanying vein are sufficiently apparent to be diagnostic Following an injury to the vessels, usually from penetrating wounds, bleeding and local swelling occur. These, as Hunter observed, may be slight or severe, depending upon the degree of runoff through the vein The characteristic *thrill* and *bruit*, synchronous with the heart beat but more intense in diastole, may not become apparent for sev-

eral days. The *pulsatile swelling, peripheral ischemia*, and *dilatation of the proximal veins* (which may pulsate) are characteristic Venous insufficiency, manifested by *edema, varicosities*, and, later, by pigmentation, dermatoses, and cutaneous *ulcerations* resembling the postphlebitic state, will also occur.

The severity of the circulatory impairment varies with the volume of shunted blood When present, failure is revealed by dyspnea and tachycardia on slight exertion, "pounding" of the heart, cardiac dilatation, and eventual death

Examination reveals the wound or its scar, the pulsatile swelling, thrill and bruit, and the pathognomonic *slowing of the pulse*, and *elevation of blood pressure upon digital occlusion of the shunt* The cutaneous temperature in the region of the fistula is elevated because of the dilatation of both arteries and veins Distal to the shunt, there may be arterial insufficiency with reduced skin temperature Venous engorgement and tortuosity, both proximally and distally, may be noted, as well as edema, dermatoses, and pigmentation. Arteriographic visualization of the fistula is possible but is usually not necessary for diagnosis

TREATMENT

Both the prevention and repair of arteriovenous fistulas have undergone dramatic changes The period in which the newer methods were instituted, with remarkable improvement in the results, coincides with the interval between the end of World War II and the outbreak of the Korean hostilities, and is a reflection of the powerful upswing in arterial surgery Credit for these advances goes primarily to the medical departments of the Armed Forces, which have had to contend with such large numbers of military injuries of important arteries They have responded to the challenge, and the lessons learned are being applied in civilian practice

For many decades, the usually recommended operation for arteriovenous fistula has been the *quadruple (or sextuple) ligation of the arterial and venous trunks proximal and distal to the lesion, and excision of the fistula* In early cases, if the severity of the systemic disturbances permitted, operation was delayed to allow the development of more adequate collateral circulation, and the sufficiency of the vascular supply to permit ligation of the principal arterial trunk was gauged by the reaction in the distal portions to temporary compression of the vessels. Elin (1946) reviewed a series of 340 cases of arteriovenous fistula from World War II, in which only 12 patients had had reparative operations. The remaining 338 had been treated by the usual method of quadruple ligation and excision None of the cases in this series ended in amputation.

A number of subsequent studies reported that although viability of the limb was usually preserved following this operation, the arterial blood supply was inadequate. Herringman (1947) found that vascular insufficiency with intermittent claudication, ischemic pain, numbness, tingling, atrophy of muscles and coldness of the extremity persisted after quadruple ligation, often to a distressing and disabling degree He emphasized that "restoration of normal arterial circulation is the primary objective of the surgeon whenever possible" Similar sequelae were described by Bosher, Harper, and Bigger, despite the added procedure of sympathectomy. In experimental studies, they demonstrated a marked regression of the collateral arterial supply following closure of a fistula. Gerbode, Holman, Dickinson, and Spencer, on the same grounds, also emphasized the desirability of restoring arterial continuity in arteriovenous fistulas, whenever it is technically feasible. Reporting from the Mayo Clinic, Foley et al. stated that a follow-up study of arteriovenous fistula of the lower extremities treated by ligation and excision revealed *arterial insufficiency* of varying degrees of severity in 50 per cent of the patients, and *venous insufficiency* in 75 per cent of the patients

During World War II, the policy of concentrating wounded personnel in special centers for treatment, according to the type of injury, was instituted, and this was continued for the casualties of the Korean War. In the management of vascular injuries, a considerable period elapsed between the time of wounding and the institution of definitive therapy, which necessarily excluded injuries of such severe grade as to make such waiting impossible. The earliest patients to reach the home base because of arterial injuries were treated by the traditional ligation techniques. Subsequently, a changeover to *arterial repairs in all major vascular injuries* was made, with immediate improvement in the results

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Cerebrovascular attacks

GILBERT H. GLASER

Diseases of the cerebral blood vessels and alterations of blood flow account for numerous acute neurologic episodes and much chronic progressive disturbance of brain function, and represent a major cause of death. A cerebrovascular attack or "stroke" is defined as *a focal neurologic disorder of abrupt development due to a pathologic process involving the vascular supply to the brain, secondary to disease of blood vessels, disturbance of blood flow, or both.* Patients recovering from "cerebrovascular accidents" are becoming an increasingly serious problem in regard to chronic care and rehabilitation. The number of these patients is increasing as the older age group becomes a greater fraction of the population. In 1955, over 175,000 deaths were recorded in the United States because of vascular lesions affecting the central nervous system, and *there are presently close to 2 million victims of cerebrovascular disease extant.* It is becoming increasingly important for the physician to be able to differentiate between the various types of cerebrovascular accidents and to determine the actual location of the involved blood vessels, so that proper initial therapy may be administered. In recent years, several new treatments have been developed, but their effectiveness is still to be evaluated thoroughly, and there is still a great need for better treatments in the acute phase, especially to control further brain damage. Also, considerations of the over-all *prevention of atherosclerosis* are paramount. The proper evaluation of these treatments is based upon a thorough knowledge of the anatomic, physiologic, and pathologic features of the cerebral circulation, and, in addition, upon the proper establishment of therapeutic investigations involving adequate controls.

CLASSIFICATION

There is still no entirely satisfactory classification of cerebrovascular diseases which will take care of both pathologic and clinical features. A classification and outline have been presented by a *Committee of the National Institute of Neurological Diseases and Blindness* (1958) which should stand as a basis for consideration. The term "cerebrovascular attack" refers to involvement of one or more blood vessels of the brain or of their root vessels by a pathologic process, producing an episode of clinical dysfunction. The pathologic process may be an abnormality of the vascular wall, *occlusion* by thrombus or embolus, change in caliber of lumen, altered permeability to plasma and blood cells, and, most important, alteration in blood flow, especially a decrease.

The following working classification of cerebrovascular attacks is modified from that of the Institute's committee.

I. Transient cerebral ischemia without infarction
   A. Recurrent focal cerebral ischemic attack (insufficiency, "spasm")
   B. *Systemic hypotension*, with syncope, focal [illegible]

II. [illegible]
   [illegible]
   A. *Thrombosis* with atherosclerosis
   B. Cerebral embolism, of cardiac or noncardiac origin
   C. [illegible]

On the basis of this experience, the immediate operative repair of vascular injuries was instituted in the Army, Navy and Marine hospitals at the battle fronts. The results proved most gratifying. The necessity for amputation in the entire series so treated fell from the previous level of 48 to 10 3 per cent. It is important that vein injury accompanied the arterial trauma in 63 per cent of the 297 patients treated by immediate surgery, and no instance of arteriovenous fistula was reported in this series (Hughes)

The treatment at the Walter Reed Army Medical Center of arteriovenous fistulas and aneurysms resulting from the Korean conflict also showed striking improvement when reparative methods supplanted the obliterative procedures (Hughes and Jahnke) A total of 215 such fistulas in 202 patients were treated in the Center, and a 5-year follow-up study was made Two-thirds of the lesions were fistulas, one-third aneurysms Most of the cases resulted from the first 2 years of the war, before the immediate repair of arterial wounds had been instituted The authors state· "After repair of acute vascular injuries became an established policy in Korea, the subsequent incidence of aneurysms and fistulas was markedly diminished"

Initially, quadruple ligation and excision was the management employed for the fistulas This entailed a delay of 3 months or longer to allow for the development of collateral circulation. Thirty lesions of major vessels, including both aneurysms and fistulas, were treated by obliterative techniques No amputations became necessary, but many patients developed arterial insufficiency, for which subsequent sympathectomy proved of little value

In order to eliminate the long preparatory period, the need for sympathectomy, and the arterial ischemia, *restoration of continuity of the major vessels* was later used instead of the obliterative methods. Division of the fistula and subsequent suture, anastomosis, or autogenous vein (or preserved artery) grafts were the means of restoring arterial continuity.

Venous insufficiency sometimes resulted from ligating the veins, and in about 30 per cent of the fistulas, simultaneous venous repair was also done. The follow-up was not sufficiently complete to permit accurate evaluation of the end results, but the impression gained was that the reparative methods were definitely to be preferred over the obliterative technique

The lessons learned from the military experience are finding application in civilian life. A striking series of four *aorta–vena cava fistulas* has been recently reported by DeBakey and his associates. Three of these were of traumatic origin, and one was due to a ruptured aneurysm All were successfully repaired, using various methods appropriate to the particular situation This and other similar reports indicate a trend in the management of vascular injuries which should largely eliminate arteriovenous fistula as a sequela. The occasional shunt that may occur, as well as those of spontaneous origin, can now be corrected, with restoration of arterial sufficiency.

Waltz et al, 1959), and hypoglycemia (Meyer et al, 1958).

Certain anatomic and physiologic factors are of importance in considering the preceding pathologic processes, and the most significant of these will be briefly reviewed. The question of *collateral circulation* involving the cerebral arterial trees still has not been completely answered The older concept was that the cerebral arteries were *end arteries* with minimal or no collaterals. Much recent anatomic work has demonstrated that *collateral arterial* circulations exist (Denny-Brown and Meyer, 1957, Meyer and Denny-Brown, 1957, Vander-Eecken and Adams, 1953), but there is still a question about their effectiveness There are at least three major anastomotic systems of vessels. (1) the circle of Willis and occasionally a *precircle connection* between the carotid and vertebral arteries (Fig 15-38), (2) the meningeal arterial anastomoses between the end vessels of the anterior, middle, and posterior cerebral arteries, and (3) an extensive capillary anastomotic network Each of these may serve, under certain conditions, to counteract the effects of focal ischemia. For example, particularly distinct anastomoses have been demonstrated between the ophthalmic and meningeal arteries, and the vertebral and external carotid arteries within 1 to 4 months after occlusion (Lehrer, 1958, Mount and Taveras, 1957). However, since encephalomalacias or relatively large areas of infarction occur in relation to occlusion or vascular insufficiency, and develop acutely, these cerebral collaterals, no matter how rich anatomically, are apparently not adequate to care for the immediate metabolic needs of the brain, and in most instances do not prevent further symptoms and ischemic necrosis. The demands of the cerebral tissue for glucose and oxygen are so great that isolated portions of the brain cannot exist without an almost completely intact circulation, and, when this is decreased to any significant extent, *infarction* usually results This is clinically important because of the vulnerability of specific areas of the brain in relation to specialization of function. The

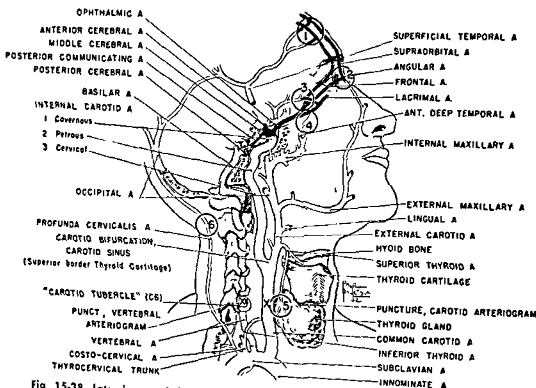


Fig 15-38. Lateral view of the circle of Willis and the cervical and intracranial carotid and vertebral arteries Anastomoses between branches of the internal and external carotid arteries are circled Sites of puncture for carotid and vertebral angiography are indicated (X). (From J P. Murphy *Cerebrovascular Disease*. Chicago, Year Book Publishers, Inc, 1954)

III. Intracranial hemorrhage, intracerebral and subarachnoid
  - A. Hypertension
  - B. Ruptured aneuryam
  - C. Angioma
  - D. Trauma
  - E. Hem[illegible]
  - F. [illegible]

IV. Hy[illegible] [illegible]ncephalopathy
  - A. Malignant hypertension
  - B. Acute glomerulonephritis
  - C. Eclampsia

The statistical *incidence of the* various types *of* cerebrovascular attacks varies *according to* the hospital series studied (*Adams, 1954; Brain, 1954; Murphy, 1954;* Gurdjian *et al., 1960*). The statistical incidence of *transient ischemic attacks* in a general *population is not* known as yet. It is believed that *at least 80* per cent of the patients with *cerebrovascular disease* admitted to hospitals have *cerebral infarction*, or *encephalomalacia*. In the past, most of these *patients* were thought to have *experienced* a *cerebral thrombosis*. However, at least one-third of them may have had *cerebral embolization* and only about one-third a *thrombosis of a large artery*. Many patients have *multiple small infarcts*, and in some *patients*, areas of infarction are present *without* evidence of gross vascular occlusion. *Massive cerebral hemorrhage is* present in 10 to 15 *per cent* of the hospitalized patients. This *disorder* may be more common, but because *of the* high *mortality rate*, many of these *patients do not* reach the hospital. About 5 *to* 8 *per cent of* patients in various series have *subarachnoid hemorrhage*. The other small-vessel *diseases* and blood dyscrasias make up the remainder.

PERTINENT ASPECTS OF PATHOPHYSIOLOGY

There has been a gradually increasing emphasis on several special aspects *of the pathophysiology of* cerebrovascular diseases. *Probably the most* important developing *concept* is that of *cerebral vascular insufficiency, hemodynamic crisis*, or *diminished cerebral blood flow* related to extracerebral factors as a *cause* of transient and recurrent neurologic symptoms (Alajouanine et al., *1960*, *Corday et al*, *1953*; Denny-Brown, *1960*; Fisher, *1958a*; Millikan and Siekert, *1955*; Rothenberg *et al.*, *1957*).

This is of particular importance when *one* considers the two emphasized sources of cerebrovascular disorders *with regard to* ves- location: the *internal carotid artery* and *basilar artery* (Denny-Brown, 1951, Fish 1951; Johnson et al., 1951; Kubik and Adam *1946*; Meyer et al., 1960, Millikan and Siekert *1955*) (*Fig. 15-38*). Another source regarde to be significant is *cerebral embolism* (Adam *1954; Fisher and Adams*, 1951; Wells, 1959) *with origin* of the embolization from (1) auricular thrombi, as in rheumatic or arterio sclerotic heart *disease with atrial fibrillation*, (*2*) bacterial endocarditis, (3) myocardial infarction with mural thrombi, and, occasionally, (*4*) atheroma in the aorta *or carotid* arteries with thrombosis It has been emphasized further that the cerebral infarction associated with *cerebral* embolism is usually *hemorrhagic*, whereas the infarction of thrombotic occlusion *is of the anemic* type.

The *totality* of the cerebral blood flow is related *to* factors of blood pressure (hypertension, hypotension, and turbulence), opposition to blood flow by variations in caliber and elasticity of the vascular tree (as produced by *localized* narrowings of the lumen, thrombosis, *embolism*, or extrinsic compression), and inherent characteristics of the blood, such as viscosity. Both generalized and localized alterations *in* blood pressure and blood flow are most significant (Denny-Brown, 1951, 1960) Those pertaining to cerebral vascular insufficiency or to hypotension in the cerebral vascular tree may be related to hemorrhagic shock, myocardial infarction, antihypertensive drugs, *postural* hypotension, the carotid sinus syndrome, anesthetics (especially spinal), cardiac surgery, sympathectomy, traumatic shock, cardiac arrhythmias (such as paroxysmal tachycardia, ventricular fibrillation, and Adams-Stokes syndrome), congestive heart failure, carotid artery ligation, and *the* progressive stenosis and occlusion of the carotid or basilar arteries, which feed the circle of Willis, usually related to atherosclerosis.

This concept of cerebral vascular insufficiency is similar to that often applied to cardiac disease in relation *to acute and recurrent* coronary *insufficiency. Distinction should* be made between carotid and basilar artery insufficiency states *due to local involvement* of these vessels and the partial or total contribution to *the* clinical picture by more general factors. such as systemic falls in blood pressure, severe

observed in man at operation when branches of the circle of Willis or other cerebral arteries were being dissected or otherwise manipulated for their exposure (Fletcher et al., 1959, Pool, 1958). Vasospasm also is regarded to be responsible for the transient "aura" associated with the *migraine syndrome* (Engel et al, 1945). However, recent investigators feel that the best explanation for transient recurring symptoms related to the cerebral circulation in most instances is not spasm but a *chronic intermittent insufficiency*, a *developing occlusion* of the internal carotid and basilar arteries, or *multiple tiny occlusions* within the cerebral substance, their repetition often being due to fluctuation in systemic blood pressure, as indicated above. Since metabolic factors appear to be most significant with regard to the local controls of cerebral circulation, attention has been paid to *hypoxia* and accumulations of carbon dioxide, especially local There are sudden falls in oxygen tension in infarcted areas, these may produce damage to the walls of capillaries and small arterioles, and thus contribute to *distal stasis* of blood cells and small extravasations (Denny-Brown, 1960, Denny-Brown et al, 1957, Meyer et al, 1957) The *Bayliss effect* may also be significant, the rapid falls in internal vascular pressures in the small vessels producing arteriolar dilatation (Bayliss, 1902) and further contributions to "stasis" *Carbon dioxide* is regarded as the most potent cerebral vasodilator (Table 15-12) and may be responsible for further vasodilatation in and around the areas of cerebral infarction Carbon dioxide is accumulated in heavy concentration in these areas and, therefore, it would appear likely that all the vessels in the involved area would be in a state of maximal dilatation This has implications for therapy.

Since our concepts of the pathogenesis and treatment of cerebrovascular disease are to be based on our knowledge of the physiology of cerebral blood flow, a review of certain significant features will be made A great deal of information has accrued concerning the general cerebral blood flow, and measurements have been made under many different circumstances by the Schmidt-Kety technique using the Fick principle (Kety, 1955, Schmidt, 1950) Of importance in these determinations is the consideration that the brain utilizes 20 per cent of the total oxygen consumption and 65 per cent of the glucose uptake of the body at rest, although it represents but 2 per cent of the body weight. The high rate of metabolic activity of the neuron has a heavy oxygen requirement, and it has been determined that if there is a total oxygen lack for, at the most, 8 min, the nerve cell ceases permanently to function and dies (Heymans, 1950) If *hypoxia* is partial, recovery of the neuron may occur even after a period of disturbed function which may have lasted for days The degree of recovery, however, is difficult to determine.

Studies of general cerebral blood flow have given the following normal values for the general cerebral circulation and metabolism in healthy young men (Kety, 1955, Schmidt, 1950), expressed as per 100 Gm/min: (1) cerebral blood flow (CBF), 54 ml, (2) cerebrovascular resistance (CVR), 1.6 units, (3) cerebral oxygen consumption ($CMRO_2$), 3 3 ml, (4) glucose consumption, 5 4 mg, (5) respiratory quotient, 0 99. This method has been applied to many experimental and clinical situations, some of these, believed to be highly significant in relation to the problem of cerebrovascular attacks, are presented in Table 15-12 (Kety, 1955). Here, the effects of various drugs, other agents or procedures, and clinical conditions on the cerebral circulation and metabolism are expressed in terms of a percentile change from normal or control values. Changes of possible statistical significance are so indicated, clinical significance, of course, has been [illegible]

[illegible] the effects produced by most drugs on cerebral blood flow are statistically not significant or only slightly so. The agent with by far the greatest effect is *carbon dioxide* It should be realized, however, that these data are gross and are concerned with total cerebral blood flow. Certainly, local changes may be of more importance but, up to the present time, techniques for the [illegible]

in [illegible]

th [illegible]

an [illegible] regulatory mechanism for the cerebral circulation, and local variations in vascular resistance certainly must occur in relation to local lesions, especially infarction The factors contributing to the property of resistance have not been completely evaluated It should be mentioned that the mechanism of action of the various drugs on the cerebral blood vessels is not known This also applies to the effects of carbon dioxide and oxygen The limitations of nerve supply imply that the effects may be intrinsic within the muscular walls, perhaps by local reflex phenomena

In this consideration of general features of pathogenesis, factors of *external compression of cerebral arteries* should be given more atten-

fact, however, that the area of infarction is usually smaller than the area of supply of that particular artery (as has been demonstrated by injection methods) suggests that there are a critical zone and a zone of shared supply. It should be noted that the anatomically significant short penetrating arteries, such as the lenticulostriate and thalamoperforating, have relatively few anastomoses and are the closest to being end arteries Their areas of supply are especially vulnerable to infarction A major question that is still not answered is that of the possible embarrassment of the collateral circulation around an area of infarction by associated "vasospasm"

Many considerations of pathogenesis and therapy center about the possible existence of *cerebral vasospasm* (Byrom, 1954; Denny-Brown, 1951; Fletcher et al, 1959, Pool, 1958). The cerebral arteriolar system is noteworthy because of the lack of significant vasomotor nerve supply and a deficient muscularis. In addition, it has been demonstrated that cervical sympathectomy or stellate ganglion block does not produce significant changes in cerebral blood flow, and that the various drugs which act upon the autonomic nervous system do not significantly alter this flow (Table 15-12, Kety, 1955). It has been shown, however, that the arterioles in the pia contract in experimental embolism, and that this contraction may be abolished by sympathectomy or block (Villaret and Cachera, 1939). This relates only to the superficial arterioles, and apparently not to those in the intracerebrovascular tree. However, so-called *cerebrovascular spasm* of major arteries *has* been demonstrated during arteriography (Fletcher et al, 1959), and widespread spasm of cortical vessels has been observed during experimental renal hypertension in rats with hypertensive encephalopathy (Byrom, 1954). Actual vasospasm has been

TABLE 15-12. EFFECTS OF DRUGS AND CERTAIN STATES ON CEREBRAL CIRCULATION AND METABOLISM (EXPRESSED IN TERMS OF PERCENTAGE CHANGE FROM NORMAL OR CONTROL VALUES)

Drug or state	*CBF*	*CVR*	*$CMRO_2$*	*MABP*
Hypertension, systemic	0	+88 *	+3	+85 *
Cerebral vascular disease †	−38 *	+150 *	−24 *	+58 *
Carbon dioxide, 5%	+54 *	−31 *	+3	+13
Oxygen, 100%	−13	+29 *	+3	+13
Oxygen, 10%	+35 *	−35 *	−6	−7
Papaverine, i v.	+15	−27 *	+12	−15
Histamine, i v	+3	−23 *	+3	−15
Aminophylline, i v ‡	−25 *	+24 *	0	−2
Aminophylline, i v §	−33 *	+46 *	−19	−5
Caffeine	−16	+31 *	+9	+9
Epinephrine	+21 *	−2	+22 *	+20 *
Norepinephrine	−9	+43 *	−5	+29 *
Differential spinal	−12	−16	−3	−25 *
Apresoline	+2	−25 *	−11	−21 *
Dihydroergocornine (DHE)	0	−28 *	+3	−24 *
Hexamethonium	+2	−30 *	0	−29 *
Tromexan ethyl acetate	−15	−26 *	+4	−34 *
Veratrum	−12	−28 *	+17	−38 *
ACTH	−5	+23 *	+8	+10
Cortisone	−2	+15	0	+12
Alcohol (blood level, 68 mg/100 ml)	+6	−10	0	−2
Bilateral stellate ganglion block	−2	+8	+3	+2

* Statistically significant change.
† Patients with mental symptoms.
‡ Normal patients

...l oxygen consumption;

sels The initial diagnostic evaluation should include, therefore, a complete history; physical and neurologic examination, blood count, urinalysis; determination of the blood sugar, nonprotein nitrogen, and electrolytes, x-ray of the skull, electrocardiogram, and an electroencephalogram The utilization of the *electroencephalogram* in diagnosis and management of cerebrovascular attacks is not mandatory but may be helpful under appropriate orientation. *Cerebrospinal fluid examination* is often extremely important from the diagnostic standpoint but should not be performed routinely. If the intracranial pressure is elevated, there

TABLE 15-13 BLOOD SUPPLY TO BRAIN AND SYNDROMES OF CEREBROVASCULAR ATTACKS

Artery	*Area of supply*	*Neurologic syndrome*
Vertebral-basilar	Posterior fossa structures: pons medulla, cerebellum; also posterior cerebral distribution (see below)	Unilateral or bilateral (1) dysfunction of cranial nerves III to XII, especially III, VI, VII, (2) cerebellar disorders, (3) motor and sensory tract signs, (4) blindness Disturbance of consciousness; patchy involvement common
Paramedian	Paramedian base of pons and midbrain, ventral pontine tegmentum	Ipsilateral paralysis of cranial nerves III, IV, VI, contralateral hemiparesis
Superior cerebellar	Lateral tegmentum midbrain, upper pons, cerebellum, middle and superior cerebellar peduncles, roof nuclei of cerebellum, lateral spinothalamic tract, descending sympathetic	Ipsilateral Horner's syndrome, cerebellar ataxia, contralateral pain and temperature deficit of face and body
Anteroinferior cerebellar (lateral pontomedullary)	Anteroinferior cerebellum, lateral tegmentum of pons and upper medulla, middle and inferior cerebellar peduncles, descending sympathetics, nuclei of cranial nerves V, VII, VIII, lateral spinothalamic tract	Ipsilateral cerebellar ataxia, pain and temperature deficit on face, Horner's syndrome, deafness, facial paralysis, nystagmus, and vertigo, contralateral pain and temperature deficit on arm, trunk, leg
Posteroinferior cerebellar (lateral medullary)	Posteroinferior cerebellum, lateral medullary tegmentum, including descending sympathetics, vestibular nuclei, spinal nuclei of cranial nerves V, IX, and X, inferior cerebellar peduncle, lateral spinothalamic tract	Ipsilateral Horner's syndrome, vertigo, nystagmus, pain and temperature deficit on face, cerebellar ataxia, paresis of palate and vocal cord with dysphagia and dysphonia, contralateral pain and temperature deficit on arm, trunk, leg
Internal carotid	Combined supply of anterior and middle cerebral and ophthalmic arteries	Ipsilateral blindness, Horner's syndrome, contralateral hemiplegia, and hemisensory deficit; dysphasia if dominant hemisphere
Ophthalmic	[illegible]	[illegible]
Anterior cerebral	[illegible]	[illegible]
Middle cerebral	Convexity of cerebral hemisphere and white matter, including lateral orbital frontal and temporal tip; perforating branches to internal capsule, caudate and lenticular nuclei, and anterior thalamus	Contralateral hemiplegia and hemisensory deficit; aphasia, agnosia, and apraxia if dominant hemisphere; syndromes often incomplete; faciobrachial monoplegia common
Posterior cerebral	[illegible] ... losum [illegible]	[illegible]

tion since they may contribute to the picture of local insufficiency syndromes (Lindenberg, 1955). The vertebral artery is particularly liable to repeated trauma and constriction by osteoarthritic, spondylitic disease and anomalies such as the *Klippel-Feil fusion of cervical vertebrae* (Ford, 1952; Hutchinson and Yates, 1956, Illingworth, 1956; Tatlow and Banner, 1957). Other anomalies, such as a prominent transverse process of the first cervical vertebra, may be contributory. Symptoms may appear during special postures, particularly flexion and turning (*postural stenosis*, Toole and Tucker, 1960). The possibility of *platelet emboli* from repeated trauma to vascular walls also may be high (Denny-Brown, 1960). *Increased intracranial pressure* may also compress blood vessels secondarily because of *herniation* of brain substance. Herniation of the temporal lobe through the incisura of the tentorium may compress the posterior cerebral artery against this structure, producing a falsely localizing *hemianopsia.* The anterior cerebral artery may be compressed by the cingulate gyrus herniating under the falx cerebri.

Peculiar anomalies of the circle of Willis also should be mentioned as occasional determining factors in the distribution of an infarction These are especially common in the vertebral-basilar system. However, some anatomic compensation does exist, and if one vessel is hypoplastic, certain related vessels may become enlarged and assume compensatory function A posteroinferior cerebellar artery may be absent on one side and compensated for by a large anteroinferior cerebellar artery One vertebral artery is often hypoplastic Hypoplasia of the posterior cerebral arteries is quite common In this circumstance, the posterior communicating artery may be large, and the entire supply of a hemisphere may be from the internal carotid

The areas of distribution of the cerebral vessels and the major clinical syndromes of neurologic involvement present in cerebrovascular attacks are presented in Table 15-13

GENERAL DIAGNOSTIC CONSIDERATIONS

Patients who have had "strokes," or cerebrovascular attacks, should not all be regarded as clinically similar from a diagnostic or therapeutic standpoint These patients often present difficult problems in diagnosis and emergency treatment, as well as in long-term management It is hoped that improved knowledge of differential diagnosis may permit use of special forms of treatment, which may limit the mortality and morbidity, particularly with regard to residual effects. Basically, these patients have had a varying degree of brain trauma and should be treated accordingly. One of the chief initial problems is the diagnosis and treatment of a patient who may be *unconscious or comatose.* Immediate diagnostic considerations are concerned with differentiating the possibility of cerebrovascular accidents from other lesions of the central nervous system, especially brain tumors and metabolic disorders, as well as an effect of trauma, such as subdural hematoma In addition, an attempt should be made to determine the particular nature of the cerebrovascular disease present.

A cerebrovascular disorder is indicated by the sudden appearance of focal or generalized neurologic symptoms in a patient with already existing cardiovascular disease, such as hypertension, arteriosclerosis, or a specific cardiac disorder (myocardial infarction or cardiac arrhythmia). Of great importance is the *history*, which should give an indication of the temporal sequence of events and a dynamic consideration of the pathologic process.

There are many variations in the pattern and severity of cerebrovascular attacks, but, in general, the patterns of development which lead to the clinical status of the patient at the time he is seen by a physician may be regarded as follows (1) *intermittent insufficiency*, transient ischemic attacks, or incipient stroke; (2) *advancing stroke*, with stepwise development (with or without transient ischemic attacks—"stuttering"), transient ischemic attacks progressing to a persistent neurologic deficit, or a gradual slow onset with minor fluctuations, (3) *completed stroke* developing as a single abrupt event in minutes or hours, with or without stuttering fluctuations, in an advancing way as described above, or, as in some instances, a completed stroke with a fixed disability but followed by further transient ischemic attacks

Steady progression of increasing neurologic signs and symptoms over a period of days or weeks without improvement usually indicates not a cerebrovascular attack but an expanding intracranial lesion There are some exceptions, however, as in gradual slow occlusion of ves-

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Posteroinf[illegible]		Horner's syndrome, vertigo, [illegible]us, pain and temperature def[illegible] face, cerebellar ataxia, paresis of palate and vocal cord with dysphagia and dysphonia; contralateral pain and temperature *deficit* on arm
Internal [illegible]		
Anterior cerebral		
Middle cerebral		hemiplegia and hemisen[illegible]; aphasia, agnosia and
Posterior cerebral	[illegible]	
	[illegible] splenium of corpus callosum	paralysis of cranial nerve III

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Steady progression of increasing neurologic signs and symptoms over a period of days or weeks without improvement usually indicates not a cerebrovascular attack but an expanding intracranial lesion There are some exceptions, however, as in gradual slow occlusion of ves-

lirium or coma, because of the cerebrovasoconstricting effect, with further diminution of cerebral blood flow (Table 15-12).

Chemoprophylaxis. Routine chemoprophylaxis of possible pulmonary or other infections is not recommended, principally because of the more serious risk of *superinfection*. The highest degree of success with *antibiotics* is obtained when they are used against specific organisms. A series of patients with respiratory distress who were *not* given routine antibiotics had a lower incidence of secondary infections than did those who *were* given routine antibiotics (Weinstein, 1955). Moreover, the types of organism in the treated group—such as *Pseudomonas*, penicillin-resistant *Staphylococcus*, and *Hemophilus influenzae*—were more difficult to combat. In addition to inducing the difficult superinfections, the routine administration of antibiotics predisposes to allergic episodes. It is concluded, therefore, that it is impossible to prevent infections completely, despite the use of potent antibiotic drugs alone or in combination. However, once an infection occurs, the actual condition should be treated with adequate doses of specific chemotherapeutic agents. The bacterial flora in the respiratory tract in patients with cerebrovascular attacks is usually mixed, and *broad-spectrum therapy* should be used.

Sedation. Many patients are restless, psychomotor behavior varies from the inactivity of *coma* or *stupor* to destructive hyperactivity in an *acute delirium*. Mild sedation by *phenobarbital* may be used but, in older patients, may cause more confusion or excitement. Difficulties in sleeping at night may be handled best with *chloral hydrate* or *paraldehyde*. *Tranquilizing drugs* of the phenothiazine group are useful, but their tendency to produce hypotension should be controlled. *Opiates should be avoided because of their depressant effect on respiration.*

Nutrition and Fluid Balance. Matters concerning the administration of fluids and food may be of extreme concern in the early phase of the illness. When the patient is in a stuporous or comatose state and unable to take any nourishment by *mouth*, *intravenous administration of fluids* becomes necessary. Occasionally, 5 per cent glucose solution in physiologic saline solution is indicated for *at least 1 to 2* liters, the remainder being 10 per cent glucose and distilled water. In some patients, *salt retention* develops, whether this has occurred should be determined by periodic estimations of serum sodium, especially when dehydration is present. Occasionally, if vomiting has been severe, *potassium deficiency* occurs. Other patients will have a significant *salt-wasting* syndrome (Welt et al., 1952) because of the secondary failure of the kidney to reabsorb salt in the proximal tubules and inappropriate antidiuretic hormone secretion. All these electrolyte alterations, particularly *hyponatremia*, may cause prolonged disturbances of consciousness and should be considered in patients who are not responding well to general therapy. In addition to electrolytes, proteins and calories are required by these patients. After the end of 1 week of ordinary intravenous salt and glucose therapy, it is usually necessary to supply up to 2000 cal per day and 0.5 to 1 Gm protein per kilogram of body weight. *Tube feeding is more efficient* than the administration of parenteral protein hydrolysate solutions. The tubes should be replaced periodically, every 24 to 48 hr. The disadvantages of leaving the tubes in place for prolonged periods are the production of increased nasopharyngeal secretions and the possibility of esophagitis.

Bladder Care. The care of the bladder is also extremely important in this acute stage. Incontinence of urine predisposes toward maceration of the skin and the occurrence of decubitus ulcers. In addition, a distended bladder may produce restlessness, otherwise not accounted for in a comatose patient. Although, in some instances, frequent changing of the bed sheets or proper urinal placement in the male may take care of the situation for 24 to 48 hr, it is usually more effective to catheterize the patient in order to prevent urinary retention and incontinence. The introduction of an indwelling catheter, however, causes bacterial invasion of the bladder and again raises the problem of *chemoprophylaxis*. However, even with routine administration of drugs, infections will occur in almost all patients. For the first 24 to 48 hr of using an indwelling catheter, open drainage is *satisfactory*; however, after this time, the catheter should be clamped off and released every 2 to 4 hr to prevent bladder contraction. It is highly recommended to use

is danger of herniation at the tentorium or foramen magnum following a *lumbar puncture*. Both *cerebral hemorrhage* and a *large infarct of the brain* may produce severe *edema* and *increase in intracranial pressure*. The findings upon lumbar puncture, however, are probably the best aid in differentiating between cerebral hemorrhage and infarction (Aring and Merritt, 1935). It should be remembered, however, that 10 to 15 per cent of patients with intracerebral hemorrhage do not have acute hemorrhage in the cerebrospinal spaces (hemorrhagic fluid), and that blood in the spinal fluid may be found in some patients with a hemorrhagic type of infarction, especially that due to *embolism*. Evaluation of *subarachnoid hemorrhage*, particularly in differentiation from meningeal infection, may require lumbar puncture Also, *cerebral neurosyphilis* may account for vascular attacks, and cerebrospinal fluid evaluation is necessary for positive diagnosis.

GENERAL CONSIDERATION OF TREATMENT

The present section is concerned with the general management of a patient with a moderate or severe cerebrovascular attack in the acute stage resulting in a disturbance of consciousness, altered respirations, and hemiplegia. Further details of diagnosis and special therapy will be given in the sections on specific types of attacks

The *immediate treatment* of a patient who has had cerebral vascular accident is devoted to maintaining life and restoring physiologic balance as best and as soon as possible The cornerstones of this treatment are based upon efficient *skillful nursing care* and *conservative expectant management* (Glaser, 1957). The patient should be placed flat in bed, and his position should be changed frequently, at least every 2 to 3 hr during the first 2 to 3 days It is extremely important during this time to prevent pulmonary complications and especially *hypostatic bronchopneumonia*

Respiratory Difficulties. Many patients have severe respiratory dysfunction in the acute stage, with stertorous breathing or *Cheyne-Stokes respiration*. *Suction* to remove nasal and oral secretions is extremely important, as is the maintenance of open airways An oral airway may be necessary; it is effected by holding the tongue and jaw forward. When choking, gagging aspirations, vomitus, or failure to cough secretions from the tracheobronchial tree interfere with breathing, the patient should lie on one side. Spontaneous coughing is easier in this position, drainage is better, and suction of the nasopharynx is more effective. The *aspiration of the nasopharynx* should be efficient, thorough, and frequent. Not only the mouth but also the posterior pharynx must be cleaned out A lubricated soft-rubber catheter should be used, and occasionally moved down far enough so that the epiglottis is touched. This may stimulate coughing and raise material from below the larynx If a major pulmonary blockage and atelectasis develop despite these measures, *bronchoscopy* should be performed In some patients, *tracheotomy* may be required The tracheotomy tube allows better suction and oxygenation.

Occasionally, *pulmonary edema* may occur, especially in patients with hypertension or coronary lesions and a tendency toward cardiac failure. This requires careful medical treatment with mercurial diuretics, parasympatholytics, digitalis, oxygen, and possibly defoaming agents.[1] *Morphine* is contraindicated, if sedation is necessary, *chloral hydrate* should be preferred. The patient with cardiac disease and orthopnea may have to remain in as convenient a sitting position as possible. This actually is not contraindicated in some patients who do not have cardiac disease and orthopnea, since the intracranial pressure is also lower in the upright posture. Many patients will require oxygen therapy following an acute cerebrovascular attack, for cyanosis often occurs as a result of inadequate breathing or cardiac failure. Either an *oxygen tent* or a *mask* is indicated Nasal catheters are not particularly recommended because they may be pulled out by the patient and, in addition, may cause necrosis of the posterior pharyngeal wall. The recommended rate of flow of oxygen is about 6 liters/min by mask and 8 to 10 liters/min in a tent in order to keep the oxygen concentration at about 45 or 50 per cent. There may be some value in adding 5 to 6 per cent *carbon dioxide* in order to produce cerebral vasodilatation, but this remains to be proved. It should be noted that oxygen concentrations of greater than 75 or 80 per cent may actually depress the arteriosclerotic patient and even cause *de-*

[1] For treatment of pulmonary edema, see also Part 18, Chap 14 *Editor.*

having had a cerebrovascular attack, and it is necessary to alleviate this fear in order to gain their maximum cooperation. This is especially true in patients having recurrent episodes.

TRANSIENT ISCHEMIC ATTACKS OR INTERMITTENT CEREBROVASCULAR INSUFFICIENCY

These attacks appear usually as recurrent warning episodes heralding the onset of a more severe cerebrovascular stroke (Brain, 1954, Corday et al, 1953, Denny-Brown, 1960, Fisher, 1958a, Rothenberg et al., 1957). They are ischemic in nature, because of alterations in local cerebral blood flow by mechanisms previously described, and are not seizures. Their main relationship is to cerebrovascular thrombosis or occlusion (*atherothrombosis*); they are, therefore, uncommon in the younger age group Most of these patients have hypertensive arteriosclerosis *Transient ischemic attacks are almost unknown prior to cerebral hemorrhage and are rare prior to a major embolic infarction.* It is important for these episodes to be diagnosed prior to the major infarction, appropriate prophylactic therapy is *anticoagulation* or *operative removal of a thrombus* followed by vascular reconstruction In cerebrovascular disease, therapy really must be preventive, treatment after a completed infarction usually has only moderate effects (Carter, 1957, 1960, Edwards et al, 1960; Fisher, 1958a, McDevitt et al, 1958; Millikan et al, 1958, Ushiro et al., 1957).

Diagnosis The signs and symptoms of transient ischemic cerebrovascular attacks usually indicate the nature of the impending infarction. Any cerebral artery, superficial or deep, may be involved, and recurrent episodes usually produce a similar pattern The attack may involve a major vessel or a minor one in strictly localized distribution The various clinical pictures are indicated in Table 15-13. In this type of attack, the brevity or transient nature of the episode is marked The duration varies from seconds to 1 hr, averaging 2 to 10 min, with no permanent residuals unless beginning infarction is taking place. The patient may experience a few attacks or hundreds, the outcome is unpredictable, as a completed infarction does not always occur The final result may be gradual, with progressively increasing neurologic deficit, or there may be a sudden precipitation The latter often occurs during sleep or shortly after the patient arises, probably because of related *hypotension*. However, often no drop of systemic pressure, directly correlated with the rapid development of symptoms, is demonstrable. Attacks also have been seemingly precipitated by exercise, emotional disturbance, heavy smoking, or bouts of coughing (Fisher, 1958a).

Transient ischemic attacks involve the vertebral-basilar vessels more often than the carotid system, and may be related to stenosing or obstructing lesions, even in the truncal vessels of supply, such as the subclavian or common carotid (Hutchinson and Yates, 1957; Meyer et al, 1960). Although vasospasm could account for these episodes, there does not appear to be any valid proof that it is a significant factor.

The differential diagnosis *should include* multiple recurrent embolism, epileptic seizures (*especially partial types*), migraine with "aura," Ménière's syndrome or primary labyrinthine disease *with vertigo, systemic hypotension* (Stokes-Adams, carotid sinus sensitivity), brain tumor, intermittent obstruction of the ventricular system, cyst of the third ventricle, small hemorrhages from basilar aneurysm, and various general symptoms appearing *in the elderly*, such as "dizziness" and akinetic *falling spells* Rare symptoms in transient ischemic cerebrovascular attacks are total loss of consciousness, major convulsive seizures, fecal and urinary incontinence, formed hallucinations, and manifestations of temporal lobe seizures.

Clear distinction should be made between *the transient* ischemic focal cerebrovascular attacks with local neurologic dysfunction, and *systemic hypotensive episodes* producing fainting or syncope with no localization of the ischemia A general hypotensive *crisis*, however, may contribute to the development of a localized cerebrovascular insufficiency, especially when there is a local vascular lesion, such as atheromatous narrowing of one of the vessels. These mechanisms have been reviewed above.

Another special *type of* ischemic episode is the "aura" of migraine, characterized by flickering scotomas, dysphasia, hemiparesis, *and* hemisensory syndromes. This [illegible]

[illegible] tree, but the mechanism is not known

tidal drainage if possible, since this definitely reduces the risk of infection.

Intracranial Pressure. Many patients have increased intracranial pressure, especially when cerebral hemorrhage is present This predisposes toward prolonged states of alteration of consciousness and, in addition, the possibility of brain herniation through the tentorium or foramen magnum. When the cerebrospinal fluid pressure is increased and the patient is comatose and dehydrated, the administration of fluids becomes difficult to adjust. In some instances the rapid intravenous administration of ordinary glucose and saline solutions will aggravate cerebral edema and raise the intracranial pressure further Lumbar puncture to reduce intracranial pressure is *not* recommended since it may cause brain herniation. Various other methods have been suggested to decrease elevated intracranial pressure but none of them is really satisfactory Intravenous administration of hypertonic sucrose or glucose solutions has been recommended. However, rebound pressure rises occur, and sucrose solution may be destructive to kidney epithelium. The use of *magnesium sulfate*, either intravenously or by proctoclysis, may be helpful, especially in hypertensive patients with severe cerebral edema. *Intravenous hypertonic urea solutions* should be administered only under careful control because of the possible development of hypernatremia and prerenal azotemia Generalized severe *headache* usually is related to increased intracranial pressure and responds to its control

Gastrointestinal Complications. Complications related to gastrointestinal tract disturbances occur in patients with acute cerebrovascular attacks. *Vomiting* may appear early and persist during the first 2 days The danger of aspiration of vomitus is great, and extensive and repeated vomiting may produce dehydration and disturbance of blood electrolytes Mild sedative therapy may be effective, as well as the use of small doses of tranquilizing drugs such as *chlorpromazine* and related substances The volume of fluid loss should be replaced if possible. If the patient continues to vomit in spite of attempts at control, the stomach should be kept empty by suction. Constant *hiccough* also may occur, especially in patients with vascular lesions of the medulla. Hiccough may be controlled by inhalations of 5 to 10 per cent *carbon dioxide* and occasionally by the administration of tranquilizing drugs, such as *chlorpromazine.* If these measures are not successful, *local anesthesia of the phrenic nerve* may be required. Rarely, some patients develop neurogenic ulcerations in the esophagus or stomach, which should be suspected if the vomitus contains blood or if the stools are tarry. Control of the patient's bowel function is also of importance in the acute phase Evacuation should be effected at least twice a week, enemas should be preferred to cathartics as they are less likely to involve soiling or severe straining

Convulsive Seizures. Occasionally, in the acute phase, convulsive seizures may occur, they are particularly frequent in patients with cerebral hemorrhage (Richardson and Dodge, 1954). A number of patients will have only one convulsion, but if recurrent seizures develop, *anticonvulsant medication* is indicated. Both *Dilantin sodium* and *phenobarbital* should be used, at first parenterally, if necessary, and then orally.

Hemiplegia. Most patients having a cerebrovascular accident develop varying degrees of hemiplegia. Usually, in the first days, the extremities are flaccid, but occasionally *spasticity* appears early within the first week The prevention of contractures is most important Correct bed positioning requires the use of a firm mattress or a board under the mattress A footboard or, better, a posterior leg molded plaster cast splint, is recommended to prevent foot drop and shortening or tightening of the Achilles tendon. Pillows are to be used under the shoulder and head to maintain good head position, and a small pillow should be placed in the axilla. To prevent contractures of the shoulder, knee, and hip, a sand bag or pillow should be placed lengthwise to relieve outward rotation at the hip, flexion at the knee, and adduction at the shoulder After the first 24 hr, the patient should have full, gentle, passive movements of all joints of the affected arm and leg, at least once or twice daily.

It is most important for the conscious patient to be reassured regarding his clinical condition This is particularly important for patients who have suffered a speech disturbance, particularly if they are still able to comprehend the spoken word However, even when the *aphasia* involves the auditory receptive functions, the patient can be reassured by the attitude of the physician. Most patients have a great fear of

particularly when there is suspicion of brain tumor or subdural hematoma *Angiography otherwise is best reserved for determining the extent and exact location of a stenotic or occlusive vascular lesion as a prelude to operative intervention* (Fig 15-40). There is increasing experience that arteriography in the older patients with hypertensive and atherosclerotic cerebrovascular disease is fraught with significant morbidity A carefully studied series recently reported had 22 per cent complications, including hemiparesis and aphasia (Baker, 1960).

Therapy. ANTICOAGULANT THERAPY. One of the major applications of anticoagulant therapy in the treatment of cerebrovascular attacks has been in these syndromes of intermittent cerebrovascular insufficiency or transient ischemic attacks involving the vertebral-basilar and internal carotid arterial trees (Fisher, 1958b, Groch et al, 1959, Millikan et al, 1955, 1958) The hope in these instances is to prevent further thrombotic occlusion of the involved vessel The patients selected for anticoagulant therapy should be nonhypertensive, although in some series the top level of blood pressure has been 200/100. Also, there should be no evidence of blood in the cerebrospinal fluid These criteria have been suggested in order to limit the possibility of cerebral hemorrhage. The evidence of the efficacy of this therapy is thus far uncertain In some series, there is distinct indication that recurrent attacks have been diminished significantly by the administration of anticoagulants and that further occlusion has been prevented (Fisher, 1958b, Millikan et al., 1955, 1958). There are many questions concerning the mechanism of action of anticoagulants in these instances, since it is felt that the anticoagulant effect as such may not be the only one (Denny-Brown, 1960, Meyer, 1958) There does not appear to be any direct interference with the process of atherosclerosis, but the anticoagulants may affect certain properties, such as blood viscosity. The anticoagulant therapy may improve the development of collateral circulation in some unknown way or limit minor embolization These may be factors, since changes in the frequency of ischemic attack may not occur for a few days.

The method of administration of the anticoagulants involves the careful use of *Dicumarol* (Fisher, 1958b, McDevitt et al, 1958, Millikan et al., 1958). Since this drug has a 24-hr latent period of action, the treatment during the first day is accomplished best by the use of *Tromexan ethyl acetate* or *heparin*, repeated to keep the venous clotting time elevated to about 20 min. The *clotting-time method* recommended is the Lee-White modification of the Howell method, which gives a normal clotting time of 5 to 8 min. Administration of Dicumarol is also started on the first day. Daily *prothrombin time tests* should be performed initially. The Link-Shapiro modification of the *Quick test*, which gives a normal time of 13 to 20 sec, is recommended. In effective anticoagulant therapy, the prothrombin time should be kept between 30 and 40 sec. The dosage of Dicumarol after the first day is adjusted according to the prothrombin time. If the prothrombin time goes above 60 sec or if hemorrhages occur, the Dicumarol should be discontinued and vitamin K should be administered It should be noted that during the first day, the prothrombin time should be determined prior to any dose of heparin, since large amounts of heparin in the blood may affect the prothrombin time value. It still has not been determined in any satisfactory fashion how long the anticoagulant medication should be administered The natural limitations of this form of therapy are great, because it requires frequent accurate determinations of prothrombin time, preferably every few days or at least once a week, and a very close long-term patient-physician relationship Often it is impractical to meet these requirements, particularly in a clinic population (Groch et al, 1959). It has been recommended that anticoagulant therapy might be used in hypertensive patients with numerous brief attacks or progressing thrombosis in addition to antihypertensive drugs. Blood pressures, for example, of 240/140 have been reduced to 180/100, at which level the use of anticoagulant therapy was regarded to be safe.

The effect of anticoagulant therapy has been variable in different series, but it is regarded by some to be particularly good in these patients with transient ischemic attacks. However, a significant number of distressing complications do occur, such as *intracerebral hemorrhage* (Barron and Ferguson, 1959) and *subarachnoid hemorrhage* and *epidural spinal hemorrhage* (Winer et al, 1959), in addition to *hemorrhagic disturbances* involving other regions of the body, such as the gastrointestinal tract and bladder (Groch et al, 1959). In a number of patients, the ischemic attacks continue, and thrombosis and occlusion develop despite anticoagulation therapy. These prob-

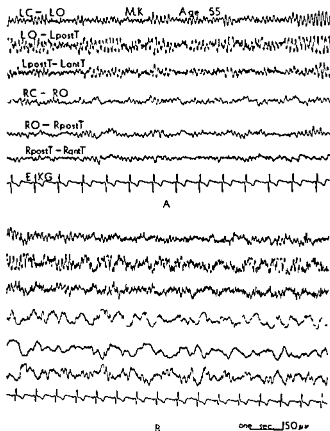


Fig. 15-39. Electroencephalograms of patient with occlusive lesion of right internal carotid artery and symptoms of right cerebral vascular insufficiency (see Fig 15-40 for arteriogram of same patient). A. Electroencephalogram in basal state Diffuse theta waves (5 to 7 cps) and disorganized, low-amplitude alpha activity from the right hemisphere, especially centrally. B. Electroencephalogram after tilting patient to 70° upright position for 5 min. Appearance of marked electroencephalographic abnormality from right hemisphere, 1 to 2 cps delta waves, especially centrally.

Certain diagnostic procedures are important in evaluating patients with transient ischemic cerebrovascular attacks *Ophthalmodynamometry* may demonstrate diminished pressure on the side of an insufficient carotid artery (Heyman et al, 1957) However, the results of this method have not been too consistent. While palpation of vascular pulsations in the neck usually is not a valuable test, pharyngeal palpation may be more effective At times decreased pulsations may be determined in the brachial vessels, indicating a general disturbance of circulation on that side Localized *bruit*, especially over the branches of the carotid artery, may be indicative of a significant partial blocking lesion (Crevasse and Logue, 1958). Compression of the carotid vessels in the neck as a testing procedure has been recommended (Gurdjian et al., 1960) but may be dangerous. Compression of an unaffected carotid vessel, for example, may result in symptoms, as the opposite vessel may be partially or totally occluded and the unaffected vessel may be the major source of supply to both hemispheres. This mechanism also may be responsible for bilateral symptoms in occasional cases of *unilateral carotid insufficiency* with both hemispheres competing for the remaining blood supply. These tests may induce convulsions or infarctions, while associated stimulation of the carotid sinus may also cause prolonged falls in blood pressure *Carotid compression tests* also have been found to be at least 20 per cent in error.

The *electroencephalogram* is usually normal in intermittent cerebrovascular insufficiency. At times, localized theta discharges may appear (Bruens et al, 1960). Occasionally, electroencephalographic recording during tilting to at least 70° may show the development of slow-wave changes over the temporal region on the side of a carotid insufficiency (Fig 15-39) and in one or both parieto-occipital regions in instances of basilar insufficiency (Meyer et al, 1956, 1957). A drop of 30 to 60 mm in systolic blood pressure usually is necessary, and the responses are found mostly in older individuals with hypertension In a number of patients, however, induced falls in blood pressure of at least 50 mm have not produced changes in the electroencephalogram or in symptoms (Weiss and Froelick, 1958).

Certain x-ray studies may be helpful An x-ray of the skull and the neck region may reveal calcification in vessels. X-rays of the cervical vertebrae may demonstrate anomalies or spondylosis which may relate to pressure syndromes involving the vertebral artery, especially associated with head turning The most significant radiologic method applied to the diagnosis of transient ischemic cerebrovascular attacks is angiography.

Because of the significant risks involved in this group, *cerebral angiography* is not to be regarded as a routine part of the medical management of patients with various types of cerebrovascular attacks (Millikan, 1960). Ideally, intrathoracic, cervical, and intracranial vessels should be visualized, but angiography to this extent often is not feasible. Occasionally, the procedure is worth performing for diagnosis

and great a fall in blood pressure may result in the production of actual cerebrovascular lesions. The rapid reduction of systemic blood pressure may produce further insufficiency in blood flow through already sclerotic and stenosed cerebral blood vessels.

Since many patients with transient ischemic [illegible]

(Nahum, 1960). Many of these patients have excessive weight, hypercholesterolemia, and hypertension. *Lipemia* may increase the tendency toward red cell aggregation in ischemic areas (Meyer et al., 1959). Other factors considered significant in this group are hypothyroidism, heavy smoking, and *diabetes*, as well as a definite family history of atherosclerosis. Reduction in blood pressure has been discussed above. In patients without significant permanent cerebrovascular lesions, the diastolic pressure should be maintained at levels of 90 mm Hg or less. Often limitation of sodium may not be accomplished merely by restriction of intake, and a drug such as *chlorothiazide* may be useful. In some patients, *aldosterone antagonists*, such as *spironolactone* (Aldactone), have been recommended. *Weight reduction* is recommended. Control of hypercholesterolemia and lipemia, which is difficult, may be attempted by the use of certain dietary restrictions (Katz et al., 1958, Nahum, 1960, Swank, 1959). This is particularly true if the cholesterol level of the serum is over 200 mg/100 ml. The diets recommended contain a minimum amount of animal and hydrogenated fats. In other diets, substitution of *vegetable oil* has been recommended. Other factors in atherogenesis that have been considered are hypothyroidism, diabetes, and estrogenic deficiencies. These disorders of hormonal imbalance should be treated by replacement therapy.

The relationship of *smoking* to atherogenesis is still not clear. There is evidence that smoking may increase the systolic blood pressure and contribute to general *hypoxia* by producing carboxyhemoglobin. There have been only the beginnings of an approach to drug therapy for atherosclerosis, and no studies have as yet been carried out in patients with transient ischemic cerebrovascular attacks. *Lipotropic agents*, such as choline, inositol, and essential fatty acids, do not lower plasma cholesterol or lipids significantly. Nicotinic acid is not recommended because of its generalized vasodilating effect. There is no evidence that pyridoxine deficiency is involved in the human disorder, but pyridoxine has been administered prophylactically. Ethylenediaminetetraacetate (calcium versenate) may lower the serum cholesterol concentration but is not effective in older patients. Newer substances which may interfere with cholesterol synthesis and be effective in human beings are awaited.

CEREBRAL INFARCTION OR ENCEPHALOMALACIA SECONDARY TO THROMBOTIC OR EMBOLIC OCCLUSION

Diagnosis. The great majority of patients with cerebral vascular accidents *who survive* the initial phase are victims of cerebral infarction or encephalomalacia secondary to thrombotic or embolic occlusion. As indicated above, the infarction may be due to *thrombotic occlusion*, *embolization*, or *progressive severe insufficiency*. Carotid artery tree involvement is suggested by unilateral extremity paralysis of a *motor or sensory nature*, associated with dysphasia and unilateral loss of vision or hemianopsia. Lesions of the basilar artery and derived branches are indicated when there are *bilateral* extremity and cranial nerve signs along with cerebellar dysfunction, bilateral disturbances in the visual fields, and alterations of *consciousness*. The various syndromes involving specific blood vessels are indicated in Table 15-13. Infarction is often preceded, as described above, by episodes of transient cerebral vascular ischemia or intermittent insufficiency, this type of progression has been described as *"stuttering,"* with increasing stepwise neurologic deficits. Occasionally, there is a sudden onset of *infarction* with a complete lesion occurring in a short period of time and producing a complete hemiplegia and severe aphasia.

The onset of *embolic occlusion* is usually sudden. Embolization may be from various sources, and the frequency of embolic occlusion is regarded to be higher than previously realized. The embolus may originate from mural thrombi in myocardial infarction, auricular thrombi in patients with fibrillation, vegetations from the valves in septic or aseptic endocarditis, atheromatous plaques and associated thrombi in the large arteries of the neck, and as fat emboli from fractures.



Fig. 15-40. Occlusive lesion (atherosclerotic) of cervical portion of right internal carotid artery, demonstrated by carotid angiography. A bruit was heard over the right carotid vessel in the neck at jaw level.

lems may limit the application of this therapy Continued detailed evaluation of this form of treatment certainly remains indicated

OPERATIVE PROCEDURES ON INVOLVED ARTERIES. In appropriately selected patients, various operative procedures have been performed in order to relieve localized stenotic and occlusive lesions (Crawford et al, 1959, Edwards et al, 1960). The specific diagnosis is made by angiography, and the patients selected are those with a history of intermittent cerebrovascular insufficiency with few if any significant neurologic residuals (Fig 15-40) The operative procedures are *thromboendarterectomy, bypassing grafts*, and various other reconstructive procedures. Lesions in the cervical portions of the carotid and vertebral vessels have been most accessible by these techniques, and the use of *hypothermia* during operation has limited the morbidity. Results have been variable but are best with lesions producing incomplete stenosis and partial occlusion. In a number of instances, anticoagulant therapy is recommended after operation in order to prevent further thrombosis of the reconstructed artery. The utilization of these operative procedures awaits further analysis and more general information concerning the interval between atherosclerotic segmental carotid stenosis and attacks of insufficiency. Such lesions are common in the vessels of persons over 50 years of age, many of whom have had no history of symptoms or signs of cerebrovascular attacks (Millikan, 1960). At present, it seems that the patients best suited for surgery are those with transient ischemic attacks without neurologic deficits and with demonstrable, unilateral, localized, incomplete lesions involving the lower portion of the internal carotid near its origin or the vertebral near its origin, both being extracranial locations Postoperative recurrence of symptoms does occur, and long-term follow-up studies are necessary.

FURTHER CONSIDERATIONS OF MEDICAL MANAGEMENT. Aside from decisions concerning the use of anticoagulation therapy and operative procedures, attention must be paid to other aspects of medical management in these patients with transient ischemic attacks. Many patients may not receive anticoagulation therapy because of the degree of hypertension or for other reasons, and the surgical approach is limited to only a small number of carefully selected patients. *Adequate treatment should include measures designed to control blood pressure, particularly low levels and hemodynamic crises* (Denny-Brown, 1960). Maintenance of an adequate degree of head pressure may be necessary to overcome the peripheral resistance of the small vessel bed This may prevent the development of neurologic signs (Shanbrom and Levy, 1957). Episodes of anemia, myocardial infarction, or gastrointestinal bleeding should receive primary attention. Many patients cannot receive anticoagulation therapy for a lifetime, and in them these other controls are of major importance. The evaluation of compressing syndromes of the vertebral vascular system, due to involvement of the cervical vertebrae, may lead to a more appropriate therapeutic approach, such as wearing a neck collar

Many patients with intermittent cerebrovascular attacks are hypertensive. The hypertension should be carefully controlled by weight reduction, administration of sedative drugs, and the use of *Rauwolfia* or its derivatives Additional help may be obtained from *low-sodium diets* and the *antihypertensive drugs*, which act as autonomic blocking agents These should be used with great care in patients with cerebrovascular attacks, since too precipitous

and great a fall in blood pressure may result in the production of actual cerebrovascular lesions The rapid reduction of systemic blood pressure may produce further insufficiency in blood flow through already sclerotic and stenosed cerebral blood vessels.

Since many patients with transient ischemic cerebrovascular attacks have atherosclerotic lesions (Baker and Iannone, 1959), attempts should be made to control this disease process (Nahum, 1960). Many of these patients have excessive weight, hypercholesterolemia, and hypertension *Lipemia* may increase the tendency toward red cell *aggregation in ischemic* areas (Meyer et al, 1959). Other factors considered significant in this group are *hypothyroidism, heavy smoking,* and *diabetes*, as well as a definite family history of atherosclerosis Reduction *in* blood pressure has been discussed above. In patients without significant permanent cerebrovascular lesions, the diastolic pressure should be maintained at levels of 90 mm Hg or less Often limitation of sodium may not be accomplished merely by restriction of intake, and a drug *such as chlorothiazide may be useful*. In some patients, *aldosterone antagonists, such as spironolactone* (Aldactone), have been recommended. Weight reduction is recommended Control of hypercholesterolemia and lipemia, which *is difficult*, may be attempted by the use of certain dietary restrictions (Katz et al, 1958, *Nahum, 1960*, Swank, 1959). This is particularly true if the cholesterol level *of the* serum is over 200 mg/100 ml The diets recommended contain a minimum amount of animal and hydrogenated fats In other diets, substitution of vegetable oil has been recommended *Other factors* in atherogenesis that have been *considered* are hypothyroidism, diabetes, and estrogenic deficiencies These *disorders* of hormonal imbalance should be treated by replacement therapy.

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Coma, convulsions, and *headache* occur in about 30 per cent of patients with these lesions. There may be elevated temperature and increased pulse rate, along with abnormalities of respiration, particularly of the *Cheyne-Stokes* type. Cerebral thrombosis or embolism may occur in the presence of normal blood pressure, but hypertension more commonly is present in patients with thrombotic occlusion. Signs of sensorial difficulty, such as confusion, disorientation, and impaired memory, are frequent after a cerebrovascular attack. In the early phase, associated with *stupor* or *coma,* the deep tendon reflexes may be hypoactive in the involved hemiplegic extremity, and, within the first 24 hr, a bilaterally positive *Babinski's sign* may be present, appearing later in the paralyzed extremity only. Other general signs may include *albuminuria,* especially in hypertensive patients, transient *hyperglycemia* and *glycosuria,* even in the absence of diabetes, and a slight peripheral *leucocytosis.* The cerebrospinal fluid pressure is usually normal in patients with cerebral embolism or thrombosis, although, rarely, pressures above 200 mm do occur Fifteen per cent of patients with cerebral embolism may have *blood in the cerebrospinal fluid* This is rare in patients with cerebral thrombosis, although there may be a slight *xanthochromia* The cerebrospinal fluid protein may be slightly elevated, but values above 100 mg are unusual The serologic reactions are negative unless the cerebrovascular lesion is due to syphilitic disease There may be a slight elevation in the number of white cells in the cerebrospinal fluid, up to 50, and higher levels may be related to septic embolization

The *electroencephalogram* may show a slow-wave focus in the involved hemisphere, usually with high-amplitude slow waves, in frequency ranges between 3 and 4 cps with severe lesions and 5 to 7 cps in the less severe (Bruens et al., 1960). Rarely, electrical activity from the involved hemisphere may be suppressed In patients with seizures or a developing seizure potentiality, sharp waves and spikes may appear from the focally abnormal regions These electroencephalographic abnormalities in cerebrovascular lesions tend to fluctuate and eventually regress toward normal *X-ray studies* of the skull usually do not show any significant abnormalities. However, they are useful to obtain when there are questions in differential diagnosis, particularly in relation to brain tumor or subdural hematoma.

The fixed cerebrovascular lesion, infarction, produced by thrombotic occlusion or embolization, must be differentiated from expanding intracranial lesions such as brain tumor, abscess, and subdural hematoma or metabolic disorders such as uremia, diabetic acidosis, and drug intoxication. The differential diagnosis is aided by a careful history and examination of the patient, as well as by studies such as urine examination, determination of blood sugar and nonprotein nitrogen, cerebrospinal fluid examination, skull x-rays, electroencephalography, and possibly pneumoencephalography, ventriculography, and angiography.

A diabetic complication is usually ascertained by the examination of blood sugar and electrolytes. The hyperglycemia of diabetes usually is much greater than the slight rises appearing with cerebrovascular attacks Uremia may merely be part of the general picture of associated chronic renal disease with hypertension and a cerebrovascular accident, but may account for many of the symptoms.

Chronic alcoholic patients may present a picture resembling a cerebrovascular attack when they are in a state of *acute alcoholic intoxication.* However, these patients, too, may have suffered a cerebrovascular accident or may have a subdural hematoma or extradural hematoma The differential diagnosis between cerebral infarction and subdural hematoma is extremely important because of the significantly good response to operation of subdural hematoma There may not be a clear history of head injury, or there may be an interval of many weeks between a relatively minor head injury and the onset of neurologic symptoms. *Subdural hematoma* should be suspected when there are fluctuations in the patient's state of consciousness, and when there is a progressive worsening in the neurologic signs and symptoms, such as increasing hemiplegia and aphasia Cerebrospinal fluid findings in subdural hematoma may be increased pressure, xanthochromia and elevated protein, and the presence of erythrocytes X-ray of the skull may reveal displacement of a calcified pineal gland There may not be significant signs or symptoms of increased intracranial pressure The electroencephalogram may be of help by revealing suppression or flattening of electrical activity over the involved hemisphere This

does not occur in all cases of subdural hematoma, and occasionally a slow-wave focus may be found If the diagnosis is seriously suspected but otherwise not confirmed, it is worthwhile to consider performing an angiogram, a bilateral trephine opening in the skull, or both. The clinical picture of brain tumor or brain abscess usually differentiates these illnesses from cerebrovascular attacks The onset is slower, and there is a more gradual, progressive development of symptoms and signs. Significant increases in intracranial pressure, papilledema, usually normal blood pressure, and increase in protein content of the cerebrospinal fluid above 100 mg/100 ml are major findings. Cerebrospinal fluid transaminase is usually not elevated in brain tumors, but may be elevated following cerebral infarction (Katzman et al., 1957). With a brain abscess, the cerebrospinal fluid may show a pleocytosis, but exceptions do occur. The electroencephalogram in these expanding intracranial lesions shows a progressively increasing enlargement of a slow-wave focus Seizures, both focal and generalized, are more common in patients with irritating expanding intracranial lesions, but they occur also in cerebrovascular accidents

The clinical course of patients with cerebral infarction is usually one of progressive improvement but with residual neurologic deficits, such as hemiplegia, hemisensory loss, dysphasia, and often some disturbance in mental functioning. Recurrences are possible, although the time interval between them may be extremely variable

In elderly patients, particularly those with hypertension and severe arteriosclerosis, small thrombotic lesions may occur repeatedly, producing multiple lacunar infarctions throughout the brain, particularly in the central white matter of the temporal and parietal lobes and the basal ganglia. There may be no severe initial dysfunction, such as hemiplegia, but progressive weakness and spasticity may develop gradually in all four extremities, along with gradual demential and pseudobulbar palsy

Cerebrovascular attacks with infarction occasionally appear in certain small-vessel diseases Thromboangiitis obliterans, or Buerger's disease, may show these complications in a small percentage (about 1 per cent) of patients (Fisher, 1957, Lippmann, 1952, Llavero, 1948). The lesions may involve the larger blood vessels, with carotid artery thrombosis, but more often, they involve the branches of these vessels, especially of the middle cerebral. The neurologic signs and symptoms are varied and usually transient before becoming permanent.

Diffuse and focal lesions of the central nervous system occur in collagen diseases, especially periarteritis nodosa and acute systemic lupus erythematosus, producing a myriad of clinical pictures with focal and generalized convulsions, dysphasia, paralyses, electroencephalographic changes, and organic mental deficits (Glaser, 1955). The cerebral lesions are secondary to proliferative and degenerative changes in the connective tissue of the smaller blood vessels leading to occlusion or rupture, with resultant disseminated ischemic changes or multiple small cerebral infarctions (Glaser, 1952).

Therapy. The general management of the patient in the acute stage following a cerebral infarction has been discussed above. Many physicians treating patients with cerebrovascular attacks become discontented with expectant conservative therapy, bed rest, and nursing care In the hope of decreasing neurologic residuals and preventing further attacks, more active treatments and procedures have been developed: vasodilating drugs, stellate ganglion block, cortisone, anticoagulant therapy, operative intervention, and the use of lysing enzymes. It may be stated at the outset that these treatments are of little or no benefit in infarction secondary to thrombotic occlusion but some of them may be helpful in the management of cerebral embolization.

VASODILATING DRUGS These drugs have been recommended in the treatment of cerebral infarction due to thrombosis, embolism, or insufficiency of circulation It has been stated already that the use of drugs which produce a generalized vasodilatation in systemic hypotension may not be effective in treating cerebrovascular disease because of the production of further cerebrovascular insufficiency due to the predominant effect of these drugs on the splanchnic vessels, causing a secondary decrease of blood flow through the brain. This result may be more disturbing than any possible direct effect of cerebral vasodilatation. Actually, the tissue metabolites in the damaged area, such as carbon dioxide, already may have produced maximal dilatation

The various drugs that have been recommended include *papaverine, histamine, Priscoline, nicotinic acid,* and *alcohol.* As may be seen in Table 15-12, the direct effects on general cerebral blood flow are not particularly significant. *Aminophylline* is not a vasodilator and may further impair cerebral circulation in patients with cardiac failure. In cerebral embolization, however, papaverine hydrochloride has been strongly recommended to control "vasospasm" in the collateral areas (Russek and Zohman, 1948). Results with this drug often are not remarkable, and there is still a need for more adequately controlled studies. *Carbon dioxide* in concentrations of 5 to 6 per cent is a most potent cerebrovasodilator, but there has been no carefully controlled investigation indicating any significant effect on the general state of the patient or on the residual neurologic deficit.

STELLATE GANGLION BLOCK The use of cervical sympathetic block has been recommended for the treatment of cerebrovascular attacks, particularly those of cerebral infarction due to thrombosis or embolic occlusion, whether the infarction be anemic or hemorrhagic (de Takats, 1954). In order for it to be effective, it has been recommended that a bilateral stellate ganglion block be performed *during the first 24 hr.* However, it has been demonstrated that this procedure does not significantly affect the cerebral blood flow in normal or hypertensive patients (Table 15-12), controlled clinical reports have shown that this procedure is not effective and does not change the chance variation of the clinical situation or the spontaneous occurrence of improvement (Millikan et al, 1953). There is the probability, already noted, that cerebral vasospasm is not a significant mechanism in the pathogenesis of these lesions

CORTISONE. Cortisone has been administered in the treatment of cerebral infarction in the hope that it would retard the development of cerebral edema, limit the tendency to herniation of large infarcts, and reduce mesenchymal tissue response to the trauma of the vascular accident (Russek et al, 1955) The steroids have been administered to patients with hypertension and diabetes without any significant complications. However, the results produced have been difficult to evaluate (Dyken and White, 1956); in general, it was regarded that the dangers of administering steroids probably outweigh any improvement that they might effect. They are not recommended as a safe means of therapy in the early stages of the usual cerebrovascular accidents. Adrenal steroids are useful in the management of these lesions in the collagen diseases (Glaser, 1955).

ANTICOAGULANT DRUGS. There is general agreement that anticoagulant therapy has no significant effect upon a completed infarction produced either by progressive severe insufficiency, with or without thrombotic occlusion, or by cerebral embolization (Carter, 1957, 1960, Fisher, 1958b; McDevitt et al, 1958, Millikan et al., 1958; Ushiro et al, 1957) However, this therapy has been recommended for the prevention of further embolization (Carter, 1957, McDevitt et al., 1958, Ushiro and Schaller, 1957; Wells, 1959). The criteria for selecting patients for anticoagulation therapy after cerebral embolization are the same as discussed above with regard to the transient ischemic attacks, and the method of administration of the anticoagulant therapy is similar There are some as yet unsolved questions concerning the timing of the beginning of anticoagulant therapy after a cerebral embolization. Experimental studies have shown that in animals with experimental embolic infarction the use of anticoagulation therapy increases the hemorrhagic nature of the infarction (Peterman et al., 1959, Sibley et al., 1957, Whisnant, 1959, Wood, 1958). Since the infarction of cerebral embolization is regarded to be a type of hemorrhagic infarction, there is the risk of increasing the already existing bleeding. It is recommended, therefore, that the anticoagulation therapy be started at least several days after the embolization in order to limit, if possible, the danger of further hemorrhage into the infarction *There appears to be adequate statistical data indicating that anticoagulation therapy prevents recurrent cerebral embolization* (*McDevitt et al*, 1958). The recurrence rate has dropped about eightfold However, there is the risk of hemorrhagic complication in the brain, as well as elsewhere in the body (see above). Cerebral hemorrhage into even an old infarction has been a significant cause of death in patients so treated (Fig. 15-41). Yet the supporters of this form of therapy feel that although this risk of hemorrhage is present, it is not excessive considering the over-all results in a large group of patients (Carter, 1957; Groch et al, 1959, McDevitt et al, 1958).

OPERATIVE INTERVENTION. Once a cerebral infarction has occurred, there are no indications that operative intervention is of benefit The responses to *thromboendarterectomy* are best, as discussed above, in patients with partial stenosing lesions and in those without completed infarction and with mainly a syndrome of transient cerebrovascular attacks (Crawford et al, 1959, Edwards et al., 1960, Millikan, 1960)

THE USE OF LYSING ENZYMES There have been a few attempts to determine the effect of lysing enzymes such as *plasmin or fibrinolysin* on thrombotic lesions (Clifton, 1958, Moser, 1959, Sherry et al., 1959), but thus far there have been no significant results pertaining to the treatment of cerebrovascular thrombosis Further studies are warranted, however.

INTRACEREBRAL HEMORRHAGE

Diagnosis. Massive intracerebral hemorrhage usually occurs in patients with systemic hypertension, but it may be caused by a ruptured aneurysm, cerebral angioma, embolization in subacute bacterial endocarditis, and the various hemorrhagic blood dyscrasias The mortality rate within the first 24 to 48 hr may reach at least [illegible]

[illegible]

bone or embolic occlusion, as described above, and is limited to an area of specific blood supply Severe hemorrhage, however, may occur in an area of infarction Intracerebral hemorrhage usually involves the cerebral hemispheres, less often, it affects the cerebellum and brain stem The onset is usually sudden but may be gradual, in most instances, the severity and intensity of the disorder reach a peak within minutes or a few hours at most Death often occurs within 2 hr Tentorial herniation is common, contributing to severe brain stem dysfunction and causing bilateral signs Hemorrhage into the cerebral hemispheres is often of sudden onset, with convulsions, severe headache, nausea, vomiting, and coma (Aring and Merritt, 1935) Hemorrhage into the brain stem, particularly the pons, has a severe onset with coma and collapse, bilateral pupillary dysfunction producing marked constriction, and extraocular palsies Respiratory difficulty, with *Cheyne-Stokes breathing*, is common Cerebrospinal fluid is uniformly bloody and under increased pressure.



Fig 15-41. Hemorrhagic infarction and intracerebral hemorrhage in region of supply of middle cerebral artery.

Treatment. Because of the high fatality rate, and since the diagnosis usually can be made with certainty in most cases, any reasonable treatment has been worth a trial Usually, only the medical management of the seriously ill and comatose patient can be offered. *There is no effective method of stopping an acute brain hemorrhage Hypothermia* has been considered but has not been used as yet in any controlled way. *Operative removal* of an intracerebral hematoma has been considered in many patients who have survived the initial shock of a cerebral hemorrhage (Davidoff, 1958). *In some instances, this procedure has proved to be lifesaving and of benefit in limiting residual neurologic deficits* However, the usually prolonged coma and the poor general state of the patient are deterrents to frequent use of operative treatment. There is some agreement now that the clinical picture most favorable to surgery consists of the sudden onset of signs and symptoms of hemorrhage in a patient who has not lost consciousness or in whom consciousness has completely returned, survival for a few days even with stupor or light coma, and then the development of progressive signs of increased intracranial pressure, such as a deepening of stupor or coma and papilledema. The surgical procedure performed in this subacute stage is either *burr hole drainage* or *evacuation of hematoma* through a *craniectomy* opening The reported operative mortality rate has ranged from 12 to 28 per cent, which is relatively low considering the high degree of mortality of the initial condition However, cases suitable for this treatment are unusual

HYPERTENSIVE ENCEPHALOPATHY

Diagnosis. Hypertensive encephalopathy is a specific acute or subacute disorder of the nervous system in patients with severe hypertensive cardiovascular disease. It is manifested by rapid elevation in blood pressure to higher levels than usual for the patient and by the occurrence of severe headaches, focal and generalized convulsions, papilledema, blindness, mental confusion, transient focal neurologic signs and symptoms, such as hemiplegia and aphasia, and the appearance eventually of stuporous or comatose states. It is usually associated with a crisis of severe elevation of blood pressure and absence of marked uremia. Massive intracerebral hemorrhage may occur eventually in severe cases Repeated episodes may produce widespread residual neurologic deficits

Hypertensive encephalopathy occurs in chronic hypertensive disease, especially associated with nephritis, as well as in acute eclampsia, acute nephritis, and some of the acute collagen diseases, such as periarteritis nodosa and lupus erythematosus.

The pathogenesis of this condition is still not clear. Necrotic arterial lesions exist in the brain, and cerebral edema occurs, with focal areas of ischemia (Pickering, 1948) It is still questionable whether focal cerebral vasospasm occurs (Byrom, 1954). However, focal small hemorrhages and occlusions are thought to be responsible

Treatment. The treatment of patients with hypertensive encephalopathy includes bed rest, lowering of the increased blood pressure, prevention of heart failure, reduction of cerebral edema and increased intracranial pressure, and the control of convulsions The withdrawal of up to 500 ml blood as an emergency measure may be effective, particularly when *pulmonary edema* is present. *Lumbar puncture* is not recommended because of the presence of cerebral edema and the danger of brain herniation *Magnesium sulfate* may be administered, intravenously or rectally, as a depressing agent The use of antihypertensive drugs has been recommended to control acute hypertensive crisis The actual dosage levels of these drugs, particularly the *autonomic blocking agents*. have to be adjusted to the individual patient and his blood pressure. Much care should be taken not to induce too precipitous a fall in blood pressure, as this may result in the production of a new cerebrovascular lesion, i e, an infarct secondary to further ischemic or anoxic encephalopathy. In some instances, where the hypertensive encephalopathy is of relatively moderate degree, effective results may be attained by *bed rest* and the use of an effective sedative, such as *phenobarbital,* which is also anticonvulsant.

SUBARACHNOID HEMORRHAGE

The primary subarachnoid hemorrhages are believed to be caused mainly by rupture of a *congenital arterial aneurysm of the circle of Willis* or by an *arteriovenous angioma* (Walton, 1956). So-called secondary subarachnoid hemorrhages are caused by *head trauma*, hemorrhagic blood dyscrasias, bleeding intracranial tumors, septic emboli, other infectious disorders of the nervous system, or intracerebral hemorrhage with leakage into the subarachnoid space. Generally, the spontaneous primary subarachnoid hemorrhages occur in a younger age group, about half appearing before the age of 40 years. Systemic hypertension and arteriosclerosis occur commonly in the middle-aged or older patients with subarachnoid hemorrhage and are contributing factors Cerebral aneurysms are common in patients with coarctation of the aorta and with polycystic disease of the kidneys.

The congenital or *berry aneurysms* usually are due to congenital weakness of the vascular wall, particularly the media, and especially at the points of bifurcation. They commonly appear at or near the circle of Willis, and vary in size up to large saccular masses, then producing symptoms by compression of the brain substance or cranial nerves. Up to 50 per cent of these aneurysms appear on either the internal carotid or middle cerebral arteries, about 25 per cent involve the anterior communicating or anterior cerebral, and about 15 per cent the basilar and its branches (McDonald and Korb, 1939, Richardson and Hyland, 1941). Rarely, aneurysms of intracranial arteries are dissecting (Scott et al., 1960).

Diagnosis. The onset of a subarachnoid hemorrhage is usually sudden, with a severe attack, characterized by excruciating *headache,* particularly involving the occipital region; collapse, signs of meningeal irritation; and the appearance of grossly *bloody cerebrospinal fluid* under increased pressure. Loss of con-

sciousness may occur quickly. Many patients develop a severe state of confusion and delirium The onset may follow exertion, but does not always do so There are usually no significant localizing signs. Hemorrhage into or irritation over the surface of the cerebral hemispheres may produce *focal seizures* or signs of localized motor or sensory dysfunction Many of the aneurysms are located near the oculomotor nerve and may produce a *third nerve palsy* In some instances, prior to the actual major subarachnoid hemorrhage, patients experience chronic or periodic *unilateral headaches*, similar to migraine and occasionally associated with diplopia and involvement of the oculomotor nerve At times, the sella turcica is eroded by a large aneurysm and symptoms of pituitary insufficiency are present Pressure on the optic nerve, chiasm, or optic tract may produce characteristic visual field deficits. In rare instances, temporal lobe seizures may occur, secondary to compression of the middle cerebral artery by a large aneurysm Seizures may be due to angioma

The signs of meningeal irritation usually are severe, with markedly stiff neck and positive *Kernig's* and *Brudzinski's signs*. Some patients complain of severe pain radiating down the lower back and legs, presumably because of blood in the lumbar subarachnoid space. Hemorrhages may appear in the retina, usually in a subhyaloid location, and slight degrees of papilledema may be present

Body temperature is moderately elevated, occasionally up to 102°F, and blood pressure is elevated This may be a result of the subarachnoid hemorrhage and not associated with previous history of hypertension A slight peripheral *leucocytosis* is common *Albuminuria* and *elevation of blood non-protein nitrogen* may occur. *Hyperglycemia* and *glycosuria* also may appear The cerebrospinal fluid pressure is often in marked elevation, to over 500 mm fluid The fluid has a uniformly bloody appearance, and there is an elevation in cerebrospinal fluid protein The number of white cells in the cerebrospinal fluid may be somewhat higher than expected from the amount of blood because of reaction to the blood Cerebrospinal fluid sugar usually is within the normal range These changes in the cerebrospinal fluid usually differentiate subarachnoid hemorrhage from acute bacterial meningitis, which may produce the same type of symptoms and signs

The natural history of the development and course of symptoms in recovery in this illness is still not completely worked out (Magladery, 1955, McKissock and Paine, 1959, Walton, 1956). The initial mortality ranges between 35 and 50 per cent, with the highest rate occurring during the first few days (over 25 per cent). Later, recurrent bleeding occurs in 20 per cent of the patients, usually within the second and third weeks, with a second 50 per cent mortality at this time. However, 60 to 90 per cent of the patients surviving the first few weeks may recover Certain factors related to recurrence are age, hypertension, and arteriosclerosis. The mortality in normotensive patients under the age of 60 is around 30 per cent, in contrast to about 50 per cent for the general group The development of neurologic deficits, such as hemiplegia and aphasia, may be related to direct effects of bleeding However, vasospasm of the vessel of origin in the aneurysm may be a responsible factor.

Treatment. The major problem in therapy of subarachnoid hemorrhage is the decision between conservative medical management and operative treatment (Magladery, 1955, McKissock and Paine, 1959, Walton, 1956). Further questions concerning the surgical approach relate to arteriography. Well-controlled comparative studies between the different forms of therapy still are not yet available. *Surgical intervention* has reduced the mortality rate in certain types of aneurysm (Botterell et al, 1958). Probably the best way to analyze this condition is to regard aneurysms of different locations as essentially separate entities In the over-all group of patients with subarachnoid hemorrhage, however, those with these selected operable aneurysms still represent a small number, and it is still not known whether an ultimate mortality rate is significantly decreased by surgical intervention (Magladery, 1955, McKissock and Paine, 1959).

There are two danger periods in relation to mortality and recurrence during the acute phase of ...

... during this period. However, it has been recommended by some groups, and with newer, more careful techniques, the risks may be limited (Pool et al, 1959). In general, the procedure is most effective if performed between the fifth and tenth days. Yet, even though it may be assumed that a congenital aneurysm is present in up to

75 per cent of patients as the cause of subarachnoid hemorrhage, arteriography, as usually performed, is positive in only 50 per cent of the group. It should be realized, in addition, that, since some patients have no localizing neurologic signs, *it may be necessary to perform three arteriograms, two carotid and one vertebral, in order to demonstrate the aneurysm.* In some instances, actually in increasing number, *multiple aneurysms* will be found bilaterally. It may be possible, by careful neurologic evaluation, to determine which of these aneurysms is responsible for bleeding. However, this usually is not so. In the past, the risks of arteriography in this group have been regarded as significant, with up to 1 per cent mortality rate, in addition to permanent complications, such as hemiplegia and dysphasia, in another 1 per cent or transient symptoms in 2 per cent of the patients. These risks have been reduced by improved techniques (Sedzimir, 1955). However, the complications still remain frequent in older patients with arteriosclerosis and hypertension up to 22 per cent (Baker, 1960). Arteriography should be performed only if surgical intervention is to be considered, or when it is absolutely required for diagnosis.

Conservative medical management is indicated when the origin of the subarachnoid hemorrhage is not a bleeding vascular anomaly or when a suspected aneurysm cannot be located arteriographically and characteristic regional neurologic signs are absent. In addition, medical therapy must be continued when (1) arteriography demonstrates an aneurysm on an indispensable or inaccessible major artery, such as the middle cerebral or basilar, and is not operable, (2) multiple aneurysms are present bilaterally, and (3) collateral circulation is inadequate through the circle of Willis as determined by preliminary carotid compression. The basis of conservative medical management is maximal strict *bed rest* in the acute stage, with rigid attention to control of breathing and adequate aeration, control of electrolyte balance, and avoidance of all forms of strain. Bed rest should be continued for at least 4 to 6 weeks after the acute bleeding stage. Many patients have systemic hypertension, and antihypertensive drugs have been recommended. While small reductions in blood pressure may be helpful, sudden drops are to be avoided. During the first few days, the symptoms of severe headache, anxiety, tension, and restlessness may require control by drugs. *Sedation* with *barbiturates* is helpful, in addition to the administration of mild *analgesics*, such as *aspirin*. If headache is severe, small doses of *codeine* or similar drugs may be administered. However, narcotics generally should be avoided because of the dangers of respiratory depression. *Lumbar puncture* should be performed for diagnostic purposes, and should be repeated mainly in order to relieve severe headache. It probably is not worthwhile to repeat lumbar puncture at intervals merely in order to reduce the cerebrospinal fluid pressure or in an attempt to prevent arachnoidal scarring. If there is evidence of intracerebral hematoma, which may be expanding or may be demonstrated by a shift of a calcified pineal on skull x-ray, lumbar puncture should be avoided.

Adequate statistical data are not yet available concerning the effect of *surgical therapy*. Since the general mortality rate with conservative medical management drops to less than 20 per cent after the first 7 to 14 days, the combined procedures of angiography and operation should produce better results than this in order to be considered worthwhile. *Internal carotid artery ligation* has been performed as a relatively safe treatment for aneurysms of this artery (Black and German, 1953); however, it often is ineffective, and there is a risk of complication, such as persistent hemiplegia and aphasia. These complications occur even though it is recommended that the ligation should not be performed unless the patient has tolerated preoperative transient occlusions of up to 15 min and, in operation, compression for at least 30 min without developing symptoms.

There are differences with regard to location of aneurysms. Aneurysm of the anterior cerebral or anterior communicating artery appears to be the most dangerous, being subject to recurrent fatal hemorrhage more frequently than any of the others. The major procedures of *craniotomy* and direct surgical approach to the aneurysm, such as *ligation* or *trapping* on both sides, have had a generally high morbidity and mortality. Emergency intracranial surgery of ruptured aneurysm in the acute stage had an immediate mortality of over 75 per cent. However, newer surgical techniques with hypothermia have greatly reduced these com-

plications (Botterell et al, 1958), and operation now has been advised during the first week, especially in order to limit the effects of vasospasm and further hemorrhage, particularly in patients under 55 years of age who are not comatose (Pool et al, 1959). These techniques have *reduced surgical* mortality to between 20 and 30 per cent. If the patient has survived 3 weeks (Norlen and Olivecrona, 1953), the risk of operation should compare with that in nonoperative management. It is, however, after this period that the risk of recurrent bleeding is much less. There still remains a great need for the accumulation of well-documented critical results from many clinics with long follow-up observations.

REHABILITATION AFTER CEREBROVASCULAR ATTACKS [2]

Patients who have had cerebrovascular attacks with infarction or hemorrhage and have *recovered after the acute stage* usually have a *hemiplegia* in varying degree, about one-half of them have *dysphasia. Hemisensory deficits* and *hemianopsia* also may complicate the picture. These conditions all represent problems in rehabilitation Hemiplegia *is neither static* nor stereotyped, it varies greatly from patient to patient The process *of recovery is a* constantly evolving series of reactions (Twitchell, 1951).

With the onset of the *hemiplegia*, the affected limbs are completely paralyzed, usually with diminution of tendon *reflexes and* flaccidity Within 48 hr, the tendon *reflexes* become hyperactive, and resistance to passive movement increases in wrist and finger *flexors* and in plantar flexors of the ankle This resistance, *or* spasticity, becomes more intense gradually and appears in other muscle groups, particularly *the flexors* and abductors in the upper limbs, and the extensors and abductors in the lower limbs. The tendon reflexes gradually become *more* hyperactive, with clonus, especially at the ankle, a positive Babinski's sign is elicited. *Voluntary* movement returns first as flexion at the shoulder and hips, later, as flexion at the elbows, wrists, and fingers, eventually as knee and ankle flexion Any attempt at willed movement results in flexor synergy, or combined flexor movements, throughout the entire upper or lower extremities. As spasticity becomes more severe, especially during the second and fourth weeks, flexion contractures develop at the hands and elbows and a tightened Achilles tendon impairs foot movements.

Physical therapeutic and rehabilitative procedures (Lowman, 1948) are begun during the first week after the cerebrovascular attack, often within the first 2 days if the patient is cooperative. These measures during the acute phase have been described above. During the next few weeks, the patient is encouraged to start a program of progressive movement. Many patients may be helped into a sitting position during the first week, and even into momentary standing This may be very effective in enabling the patient to maintain a sense of body position. While in bed, the patient should be able to exercise the upper and lower extremities with overhead pulleys *and ropes in* order to reestablish patterns of reciprocal motion In addition, quadriceps-strengthening exercises *and active exercises* of the arm muscles are instituted in order to reestablish normal patterns of movement. It is recommended that the patient begin self-care activities, such as *feeding*, washing, and dressing, as early as possible. If the patient is dysphasic, attempts at *speech therapy* should be started shortly after initial evaluation of the deficit. *The* results of properly applied techniques of rehabilitation in patients with chronic effects of cerebrovascular accidents, such as hemiplegia, show *that* about 85 per cent of these patients will *be able* to walk and take care of themselves generally, and that over 30 per cent will be able to become gainfully employed

Many patients have severe problems of *psychologic deficit*. Lesions of the dominant hemisphere cause dysphasia, alexia, agraphia, and agnosia, with disturbing, often slow, and varied recovery rates (Wepman, 1951). Many patients experience a *syndrome of denial*, either of part of the involved side of the body, or of the fact that the part is paralyzed, especially during the early phase of the accident This form of denial, which occurs particularly in patients with *a minor hemisphere lesion*, has been called *anosognosia* In other patients with major or minor parietal lobe involvement, a cortical sensory deficit with loss of acute discriminating powers makes the use of the extremity in physical therapy most difficult. Brain damage produces both qualitative and quan-

[2] See also Part 20, Chap 3. *Editor.*

titative deficits in intellectual functions, and often it is worthwhile to determine the intensity of these deficits by *psychologic testing*. Projective tests of personality structure and emotional reactions also may be of benefit. The preillness personality configuration and resources of the patient generally determine his reaction to his disabilities and his response to a rehabilitation program. Brain damage may produce, in addition to a language or comprehension disturbance, confusion, affective disturbance, such as depression and irritability, compulsiveness, and many secondary somatic complaints. These may increase during times of stress when new responsibilities and activities are added in the program of rehabilitation.

Factors that complicate or prolong recovery and limit the extent of rehabilitation, therefore, are marked *spasticity*, severe *sensory deficit*, prolonged *flaccidity of extremities*, continued *disorientation and confusional states*, pre- and postillness *personality problems*, and certain medical complications such as pulmonary, cardiac, or renal disturbances. It is best to adapt the rehabilitation procedures to the individual, with but a few general rules. The program should be supported by a complete hospital team, involving physician, nurse, physical therapist, and social worker The family must be brought into the situation and should be reassured and encouraged along with the patient The tasks given to the patient should proceed from the very simple, while he is in bed, to the more complex tasks, such as carrying out the activities of daily living, without exceeding at any time the ability at the moment to perform these tasks The patient should be placed on a program of increasing self-attendance and self-responsibility. Often the use of mild sedatives, such as barbiturates and stimulants, is helpful In addition to the described activities of physical therapy, a daily schedule of recreation, social contact, and occupational therapy should be organized

Patients with *embolic cerebral infarction* secondary to cardiac disease with atrial fibrillation often are limited in their physical rehabilitation by diminished cardiac reserve and by the danger of recurrent embolization. In such patients, atrial fibrillation has been converted to regular sinus rhythm by *quinidine* Significant improvement in hemodynamics and clinical efficiency then occurred (Sokolow et al., 1956).[3]

The problem of *spasticity* is extremely important; there is still no really effective physical or pharmacologic means of relieving the state maximally in order to improve the function of the involved extremity. Spasticity, primarily due to hyperactivity of proprioceptive reflexes, is the primary factor in the production of severe flexion contractures in the upper extremities and of extensor fixations in the lower extremities. In addition, *ankle clonus* appears along with spasticity, often interfering greatly with the ability of the patient to apply pressure and to support himself on the involved lower extremity. The more or less fixed position of the foot in plantar flexion produces a tendency to tightness and shortening of the Achilles tendon, which is difficult to relieve, except by stretching and surgical procedures. Certain "antispastic" drugs have been developed but are still in the process of evaluation. Their effectiveness following oral administration is minimal, but they may relieve spasticity enough in some patients to enable more effective mobility. The drugs in this group are *Myanesin*, *Paraflex*, *Robaxin*, and *Trancopal*.

Soon after a cerebrovascular attack, as the patient becomes aware of his general condition, it is worthwhile to present to him and his family a definite plan of self-care and eventual ambulation It has been stated that if a patient can move his arms slightly or raise his affected leg at least 1 in. from the bed, he will be able to walk again As soon as the medical situation warrants (which is generally within 10 days to 2 weeks), the patient should make attempts to walk. Being able to stand erect and to begin walking exercises has a great effect on morale. Preliminary walking with parallel bars is a safe, easy method of developing correct walking patterns with reciprocal motion. The usual hemiplegic patient will learn to walk outside the bars with one cane and will usually continue to use one cane Actual crutch walking probably will not be necessary. When not involved in walking exercises, the patient should be sitting in a wheelchair, eventually he should be allowed to push his own chair. Because *wheelchair contractures* de-

[3] Another significant step is the use of anticoagulants (see Part 21, Chap. 13). *Editor.*

velop so rapidly, in both the affected and unaffected legs, no patient should spend the entire waking day sitting in a wheelchair or in any other chair. Wheelchair contractures are 90° knee flexion contractures with shortening of the shorter hamstring muscles and consequent stretching and weakening of the quadriceps muscle. Exercises of the quadriceps muscle are extremely important. This muscle must be kept strong enough, if possible, to lift the leg against gravity, otherwise, the knee will buckle as the patient stands. Many patients (up to 60 per cent of them) will need some type of support for the paretic leg—either a short leg brace with a foot drop attachment, or a long leg brace with foot drop correction and lock at the knee. These braces are not to be ordered until at least 3 months after the onset of the cerebrovascular attack, when it becomes apparent that muscle return will be insufficient for stable walking. Temporary bracing may be used in the interim.

For the upper extremities, *forearm splints* may be applied, with dorsiflexion or "cock-up" support, and often with elastic bands for finger exercises. The hand and fingers also may be exercised well with a rubber ball.

The activities of daily living involve those of caring for one's self in bed, eating, dressing, and using utilities and communications. Later on, the patient is taught to walk up ramps, around curbs, up stairs, and across streets, and, progressively, to get in and out of automobiles and public conveyances. Care should be taken, however, to work within the limits of fatigue of the patient; an elderly patient's attention to cardiac status is important.

Emphasis, therefore, in rehabilitation, is first on the development of activities of daily usefulness and living. Concentration then is usually on the lower extremity because of the importance of walking. Upper extremity involvement is more difficult to treat, since it may be less responsive in recovery and since fine movements in the fingers most often do not recover significantly. There are certain limits that should be considered. Usually there should be some response during the period of 4 to 6 months of intensive treatment within an out-patient or hospital setting. An intensive program may be dropped after this, although some treatment should be continued for 6 to 18 months.

Chronic pain syndromes may develop in the hemiplegic patient. Some of these are related to the contractures caused by spasticity and will respond partially to the administration of analgesics and antispastic drugs, and to physical therapy in the form of warm moist applications and baths. Fixations of the shoulder and hand may be painful, in these instances the best therapy is really prevention by early institution of passive and active motions. In some patients a *thalamic syndrome* associated with the hemiplegia results in spontaneous pain and burning sensations (*thalamic pain*), which often are unbearable. The therapy in these situations is extremely difficult; no form of treatment has been satisfactory. However, spontaneous improvement is relatively common.

titative deficits in intellectual functions, and often it is worthwhile to determine the intensity of these deficits by *psychologic testing*. Projective tests of personality structure and emotional reactions also may be of benefit. The preillness personality configuration and resources of the patient generally determine his reaction to his disabilities and his response to a rehabilitation program. Brain damage may produce, in addition to a language or comprehension disturbance, confusion, affective disturbance, such as depression and irritability, compulsiveness, and many secondary somatic complaints. These may increase during times of stress when new responsibilities and activities are added in the program of rehabilitation.

Factors that complicate or prolong recovery and limit the extent of rehabilitation, therefore, are marked *spasticity*, severe *sensory deficit*, prolonged *flaccidity of extremities*, continued *disorientation and confusional states*, pre- and postillness *personality problems*, and certain medical complications such as pulmonary, cardiac, or renal disturbances It is best to adapt the rehabilitation procedures to the individual, with but a few general rules The program should be supported by a complete hospital team, involving physician, nurse, physical therapist, and social worker The family must be brought into the situation and should be reassured and encouraged along with the patient The tasks given to the patient should proceed from the very simple, while he is in bed, to the more complex tasks, such as carrying out the activities of daily living, without exceeding at any time the ability at the moment to perform these tasks The patient should be placed on a program of increasing self-attendance and self-responsibility Often the use of mild sedatives, such as barbiturates and stimulants, is helpful In addition to the described activities of physical therapy, a daily schedule of recreation, social contact, and occupational therapy should be organized

Patients with *embolic cerebral infarction* secondary to cardiac disease with atrial fibrillation often are limited in their physical rehabilitation by diminished cardiac reserve and by the danger of recurrent embolization In such patients, atrial fibrillation has been converted to regular sinus rhythm by *quinidine* Significant improvement in hemodynamics and clinical efficiency then occurred (Sokolow et al., 1956).[3]

The problem of *spasticity* is extremely important, there is still no really effective physical or pharmacologic means of relieving the state maximally in order to improve the function of the involved extremity. Spasticity, primarily due to hyperactivity of proprioceptive reflexes, is the primary factor in the production of severe flexion contractures in the upper extremities and of extensor fixations in the lower extremities. In addition, *ankle clonus* appears along with spasticity, often interfering greatly with the ability of the patient to apply pressure and to support himself on the involved lower extremity. The more or less fixed position of the foot in plantar flexion produces a tendency to tightness and shortening of the Achilles tendon, which is difficult to relieve, except by stretching and surgical procedures Certain "antispastic" drugs have been developed but are still in the process of evaluation. Their effectiveness following oral administration is minimal, but they may relieve spasticity enough in some patients to enable more effective mobility. The drugs in this group are *Myanesin, Paraflex, Robaxin,* and *Trancopal*

Soon after a cerebrovascular attack, as the patient becomes aware of his general condition, it is worthwhile to present to him and his family a definite plan of self-care and eventual ambulation It has been stated that if a patient can move his arms slightly or raise his affected leg at least 1 in. from the bed, he will be able to walk again. As soon as the medical situation warrants (which is generally within 10 days to 2 weeks), the patient should make attempts to walk Being able to stand erect and to begin walking exercises has a great effect on morale Preliminary walking with parallel bars is a safe, easy method of developing correct walking patterns with reciprocal motion The usual hemiplegic patient will learn to walk outside the bars with one cane and will usually continue to use one cane Actual crutch walking probably will not be necessary. When not involved in walking exercises, the patient should be sitting in a wheelchair, eventually he should be allowed to push his own chair. Because *wheelchair contractures* de-

[3] Another significant step is the use of anticoagulants (see Part 21, Chap 13). *Editor*

CLINICAL MATERIAL

Table 15-14 summarizes the authors' experience with 146 patients operated upon for cerebral arterial insufficiency during the past 4½ years. The majority of these patients had occlusion of the proximal end of the internal carotid artery. *Carotid endarterectomy* was possible in all patients with partial occlusion. *Removal of the thrombus* and restoration of cerebral flow were accomplished in 3 of 8 patients with complete occlusion of the internal carotid artery. Eight patients were treated for occlusion of the vertebral artery, blood flow was restored in 7 of them. Bypass Dacron grafts were required for occlusion of the innominate and common carotid arteries in 13 patients. All these grafts have remained patent. Eleven of this group have been followed for 2 to 4 years In addition to these patients, 10 others had explorations of the neck for a suspected lesion of the carotid bifurcation. No significant lesion was found. It was assumed that in these 10 patients occlusive lesions were intracranial

Table 15-14. Summary of Data on 146 Patients with Cerebral Arterial Insufficiency

Location of lesion	No of patients	Incomplete occlusion	Complete occlusion
Internal carotid arteries	123	115	8
Vertebral artery	8	7	1
Common carotid artery	10	2	8
Brachiocephalic artery	3	0	3
Carotid exploration *	10	0	0

* In addition to these 146 patients, 10 others had explorations of the neck for a suspected lesion of the carotid bifurcation No significant lesion was found.

PATHOLOGY

Arteriosclerotic occlusive lesions of the carotid and vertebral systems have a characteristic topography. According to Adams and Fisher (in press), atherosclerosis implicates arteries 0 2 mm or more in diameter Branching, junction, and curves are favored sites for the formation of plaques Identifiable plaques rarely appear in vessels less than 0 2 mm in diameter The cervical portion of the internal carotid artery was shown to be the earliest and most consistent part of the vascular system to be involved. Atherosclerosis renders the arteries susceptible to several pathologic changes which are of critical importance to the circulation of the brain As the lumen of the artery becomes narrowed, the blood flow through the vessel is reduced Symptoms are not produced, however, until a critical point is reached, when collateral circulation is inadequate or when it is altered, because of a temporary episode of hypotension, cardiac failure, or change in blood viscosity The intima gradually thickens and ulcerates, and finally leads to thrombosis. The cerebral lesions that follow upon thrombosis exhibit wide variations, depending on the location of the lesion, collateral vascular channels, and probably other factors, such as level of blood pressure, degree of vasoconstriction. and extent of propagating thrombus. It is well known that after gradual occlusion of a major cerebral artery in the neck, collateral circulation develops via the circle of Willis. The importance of this system has been adequately demonstrated by angiographic studies. Anatomic experiments by Vander-Eecken and Adams (1952, 1953) have shown that in the human brain there are direct pial arterial anastomoses between all the major cerebral vessels which provide additional collateral circulation distal to the circle of Willis Repeated angiograms at intervals following carotid ligation show that these collateral vessels are capable of a great increase in size in a matter of weeks. There are also direct end-to-end anastomoses between the tributaries of the cerebellar arteries and the posterior cerebral artery, which provide collateral circulation when the basilar artery is occluded. From these studies it is apparent that in patients with multiple occlusive lesions restoration of flow in one branch may result in improvement of general circulation of the brain through the above-mentioned collateral channels In the authors' group of 146 patients, 123 had occlusion at the carotid bifurcation. Figure 15-42 demonstrates other occlusive sites amenable to surgical correction Although complete occlusion of the internal carotid and vertebral arteries may occur insidiously, it is usually associated with a typical group of symptoms recognized as a "stroke" If the collateral flow is inadequate, brain infarction develops shortly after occlusion becomes complete, and the damage becomes irreversible. As the origin of the internal carotid or vertebral artery becomes blocked, the thrombosis progresses distally and

1

Surgical management of cerebral arterial insufficiency

HUSHANG JAVID AND WILLIAM S. DYE

The increasing prevalence of cerebrovascular accidents resulting from atherosclerotic occlusion has created serious social and economic problems. According to a study made by Meyer et al. (1955), 33 per cent of all autopsies performed showed a significant degree of cerebrovascular disease. A similar study by Adams and Vander Eecken revealed the incidence to be 20 per cent of all necropsies. A careful study of 1,018 patients by Robinson et al. showed that the initial attack of cerebral thrombosis was fatal in 21 per cent of cases. Fifty per cent of the 747 patients who survived one episode of thrombosis died within 4 years; only 18 per cent of a comparable sample of the general population died within the same period Adams et al. (1957) demonstrated that in patients dying of cerebral thrombosis, transient ischemic attacks were present prior to the final episode in 53 per cent In 18 per cent "stroke" came on in a stepwise manner, with or without transient cerebral ischemia In only 17 per cent of patients was the stroke a single event According to these and other studies, it seems apparent that the majority of patients who develop cerebral thrombosis or die from it have had adequate warning to permit recognition of a vascular occlusion before the final attack occurs

The most common cause of *cerebral thrombosis* is arteriosclerosis. The significance of this lesion in patients with cerebral arterial insufficiency was recognized by Chiari (1905) and by Hunt (1914). Involvement of brachiocephalic branches by atheromatous lesions was described by Broadbent (1875) and by Penzoldt (1881). Chiari emphasized the frequency of atherosclerotic changes of the carotid bifurcation and thought that the cerebral symptoms associated with this lesion were due to embolic phenomena. Advanced stages of occlusion of brachiocephalic branches were described by Takayasu (1908). He noted *a syndrome characterized by loss of pulsation in the arteries of the upper extremity, associated with syncope, visual disturbances, and changes in cerebral function.* The majority of his patients were young Japanese women. The occlusion was considered to be due to inflammatory process. Martorell and Fabre (1944, 1954) described the clinical picture of occlusive lesions of the aortic arch branches. Fisher (1954) reported 45 carotid artery occlusions among 432 autopsies on chronically disabled veterans He found that in spite of severe involvement of the carotid bifurcation, the intracranial vessels were relatively free of disease. This and other observations led to the application of operative procedures that had proved effective in other segmental arterial occlusions Eastcott et al reported the first successful reconstruction for carotid occlusion which resulted in relief of symptoms. Since that time, direct arterial surgery has been employed with increasing frequency in the treatment of cerebral arterial insufficiency.

carotid and vertebral systems. These patients, in the opinion of the authors, deserve correction in multiple stages. Results are gratifying.

DIAGNOSIS

Occlusive lesions of the carotidovertebral system usually occur in two general areas, the origin of the internal carotid artery and the vertebral artery. Proximal lesions, involving branches of the aortic arch, may produce ischemic manifestations of the upper extremities in addition to cerebral vascular insufficiency. These lesions are readily diagnosed by physical findings. A diminished carotid or subclavian pulse, or the absence of one, immediately draws attention to the involvement of the *brachiocephalic branches.* When neck pulses are normal, differentiation between the intracranial cerebrovascular disease and occlusive lesions of the internal *carotid* and *vertebral* systems at the neck level often becomes difficult. A vascular lesion should be suspected when the following features are presented by the patient: (1) attacks of transient cerebral insufficiency, (2) rapid reversal to normal, (3) signs of atherosclerosis elsewhere, (4) hypertension and diabetes mellitus, (5) preservation of consciousness in the presence of a significant neurologic deficit, (6) onset of symptoms at rest or upon rising (state of hypotension).

Symptoms of carotid insufficiency *differ to* some degree from those of vertebral-basilar insufficiency. Patients with *carotid insufficiency* usually experience blurring of vision or temporary blindness on the side of occlusion, associated with hemiparesis or hemiplegia on the opposite side. Aphasia is present *when the left* carotid is involved. Light-headedness is the most common complaint. *Vertebral insufficiency* is manifested by vertigo, double vision, bilateral dim vision, ataxia, and other bilateral neurologic abnormalities.

Physical examination is most helpful in localizing the offending lesion by *revealing*

1. Diminished common carotid *pulsation with bruit* over the base of *the neck, this* indicates occlusion of the *proximal* end of this vessel.

2. Diminished common carotid pulsation without *a bruit,* this may occur in complete internal carotid *occlusion.* Since the flow through this artery is decreased, the pulsation appears diminished.

3. *Bruit* over the base of *the neck* without transmission along the carotid or subclavian vessels, this may be the result of stenosis of the vertebral artery.

4. Palpation of a firm nodule at the level of the carotid bifurcation accompanied by a bruit is highly suggestive of an occlusive lesion of the internal carotid artery. A bruit may be missing in the presence of relatively mild or extremely severe stenosis. A continuous bruit was noted in several patients with marked narrowing of the internal carotid artery and inadequate collateral supply.

5. Palpation of the internal carotid artery through the tonsillar fossa should be attempted, as it may be of help in the diagnosis in some patients. This is not consistently successful, however, since transmitted pulsations from the external carotid artery may render the examination unreliable.

6. *The superficial temporal artery pulsation* may be diminished in *advanced carotid bifurcation lesions,* or it may be increased in cases of *internal carotid occlusion due to increased* compensatory flow.

7. *Carotid compression* may result in *syncope* or *convulsive seizure,* suggesting significant narrowing *of the* opposite carotid artery.

8. *Ophthalmodynamometry* may reveal a reduced *pressure* in *the* central retinal artery, providing a reliable sign. This examination requires considerable skill and, even in the hands of an experienced examiner, has certain limitations. Severe occlusive lesions have been demonstrated arteriographically and at operation in patients in whom the retinal artery pressure was thought to be normal.

9. *Angiography* is most helpful in making the accurate diagnosis of the location and the *degree of* arterial disease. In about 40 per cent *of the patients* who have symptoms of cerebral arterial insufficiency, occlusive lesions can be demonstrated *in* the major arteries supplying the brain. Three methods have been used to visualize brachiocephalic branches.

1. *Intravenous angioaortography.* After introduction of 90 per cent Hypaque solution into the superior vena cava or right atrium, serial pictures demonstrate lesions of aortic arch branches and at times permit visualization of vertebral and internal carotid arteries.

2. Retro...

(Fig. 15 ... ...ation, and cerebral branches

...nt Hypaque solution

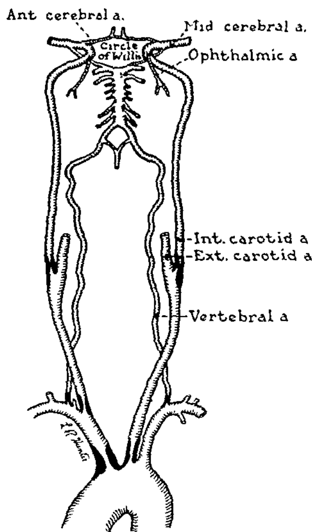


Fig. 15-42 Common sites of occlusive lesions of the carotid and vertebral system

terminates at the level of the first large branch. After the thrombus has become organized, clearing of the vessel is surgically impossible It is, therefore, extremely important to become familiar with the clinical picture of *cerebral arterial insufficiency* resulting from stenosis of these arteries if the aim is prevention of cerebral infarct

CLINICAL FEATURES

Clinical manifestations of cerebral arterial insufficiency are variable and depend upon the location and extent of the lesion Although classification of patients with cerebrovascular disease is difficult because of the complexity of symptoms, the authors have, for the sake of convenience, divided their group into three categories

Category I. Patients in this group usually experience *intermittent attacks*, which differ to some degree, depending upon whether the carotid or the vertebral system is involved. These patients usually recover from this so-called *little-stroke syndrome* spontaneously and show no evidence of residual abnormality. Episodic loss of function, which is supposedly ischemic, is due not to sudden vascular occlusion but to temporary failure of the compensatory mechanism. The cause of this transient deficit is not well understood, although alteration in the blood pressure (Corday et al.) and viscosity of blood (Millikan et al.), changes in local carbon dioxide concentration (Johnson), cerebrovascular resistance, and *embolic phenomena* (Chiari) have been suggested. It is well understood, however, that increase of carbon dioxide, decrease of oxygen, or decrease of pH causes decreased cerebrovascular resistance, resulting in increased flow and correction of local ischemia. This may play an important role in the recovery after transient ischemic episodes. Patients in this category exhibit *partial occlusion of the internal carotid artery or vertebral artery* and, therefore, are amenable to surgical correction. Several of the authors' patients in this category had *complete occlusion of the brachiocephalic or common carotid artery* and responded well to corrective surgery.

Category II. The majority of patients in this group have a longer history of intermittent cerebral ischemia. In addition, they present the picture of a "stroke" resulting from *cerebral infarct*. Although recovery occurs, often some residual neurologic abnormality persists It is most discouraging to treat patients in this group When the clinical picture denotes brain damage, operative procedure is ineffective in correction of cellular damage. *Thrombectomy* may be indicated shortly after occurrence of the stroke in order to restore blood flow and improve the prognosis for protecting other parts of the brain

Category III. The diagnosis in this group of patients presents a great challenge. Symptoms are usually varied and vague, and are slowly progressive over a period of many months *Dizziness*, loss of efficiency, impairment of memory and concentration powers, and generalized muscle weakness are among the most common complaints *Visual disturbance* is common and may include visual field defects. These patients are in the older age group and have evidences of generalized arteriosclerosis of many years' duration. Study, as a rule, demonstrates *multiple occlusions of the*

Surgical intervention in the presence of acute occlusion of the carotid artery is often disappointing. If surgery can be performed shortly after occlusion occurs, it may be possible to remove a fresh thrombus and correct the narrowing by a *local endarterectomy* The use of *heparin* solution for irrigation of the internal carotid artery under low pressure may also be helpful in evacuating the internal carotid artery. It has been the authors' experience, however, that when the hemiplegia is established, clearing of the thrombosed artery does not affect the speed of recovery. Restoration of blood flow may be of benefit in improving the prognosis of the patient, since other brachiocephalic branches may become occluded in time

Occlusions of the common carotid artery, innominate artery, and subclavian artery have been treated with a *bypass procedure* in 13 patients The use of a crimped Dacron graft bypassing these occlusive lesions has proved most satisfactory. A *graft* between the ascending arch of the aorta and the common carotid artery has been used in four patients with lesions of the innominate artery. Four patients with left common carotid occlusion were treated with bypass grafts between the left subclavian and left common carotid arteries. In two patients, a bifurcation graft was used to bypass occlusions of the left common carotid and left subclavian arteries in one person, and of both common carotids in the other. Three remaining patients had significant occlusion of the left common carotid artery and its bifurcation, in addition to severe stenosis of the left subclavian artery. A Dacron tube between the ascending arch and the left internal carotid artery was used in these patients. The ascending arch of the aorta is approached through a midsternotomy incision; the subclavian artery, through a transverse supraclavicular incision

Extreme care must be exercised during dissection in order to eliminate embolic lesions in those patients in whom atheromatous substances may adhere loosely to the wall of the artery. Occasionally, thickening of the intima extends distally and involves a significant portion of the internal carotid artery It is appropriate in such a situation to be content with a *limited endarterectomy* and to enlarge the lumen with a *patch graft* When the intima is thickened and adheres poorly to the outer wall, interrupted sutures may be necessary to

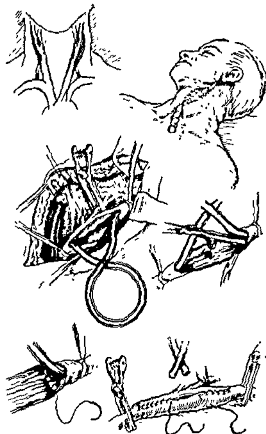


Fig. 15-45. Steps of carotid endarterectomy under local anesthesia using a temporary bypass shunt.

secure the intima to the wall and prevent its dissection Postoperative *anticoagulant therapy*, in the form of subcutaneous heparin administered every 6 hr, has been used for temporary periods up to 1 week. Hypotensive episodes occurring during surgery or in the postoperative period should be treated promptly and energetically.

Results of Surgery. Surgical results are tabulated in Table 15-15. Three patients died in the immediate postoperative period: *myocardial infarct* was the causative factor in one death, and *cerebral infarct* in the other two Unilateral neurologic deficit developed in four patients *Muscle weakness* of the arm was noted immediately following surgery in three patients, despite patency of the endarterectomized segment. Paresis in these patients gradually resolved A hypertensive, diabetic, middle-aged man developed *hemiplegia* and *coma* 2 days after carotid endarterectomy. Spinal puncture revealed the presence of blood in the spinal fluid Response to hypothermia and urea



Fig. 15-43. Percutaneous carotid arteriogram showing marked stenosis of the proximal end of the internal carotid artery with irregularity of the carotid sinus.

has been used in well over 100 cases without any harmful effect.

3. *Percutaneous subclavian arteriogram* is the most satisfactory method for visualizing the proximal end of the vertebral artery.

TREATMENT

Since therapeutic measures are of no benefit when a fully developed cerebral infarct has been established, it is most essential that emphasis be placed on prevention. Fundamentally, this means the eradication of atherosclerosis. Until this is achieved, every attempt should be made to recognize vascular lesions in their preocclusive stage and correct them surgically. The use of *anticoagulants*, although often effective, has certain limitations. It depends upon collateral circulation and preventing extension of the occlusive process. Unfortunately, many of these lesions are multiple, therefore, development of collateral channels is limited. Furthermore, the arteriosclerotic changes are progressive, and complete obstruction eventually takes place in spite of anticoagulant treatment.

Restoration of blood flow has been possible in all patients in category I. Partial occlusion of the internal carotid or vertebral arteries has been treated by *local endarterectomy*. Carotid bifurcation is readily approached through a longitudinal incision in the neck under local anesthesia. Atheroma is removed by careful separation of the intima from the outer wall of the artery (Fig. 15-44). In patients who have multiple occlusions, and in those who do not tolerate compression of the carotid artery, a *temporary internal shunt* is used (Fig. 15-45). Occasionally the carotid sinus is narrow and the use of an *autogenous vein patch* or a *prosthesis* is necessary to provide adequate lumen. Lesions of the proximal end of the vertebral artery may also be approached through a neck incision, but because of the depth of dissection, general anesthesia is preferred. The use of *local endarterectomy, arterioplasty,* and an *autogenous vein graft patch* is often necessary to correct the involved segment.

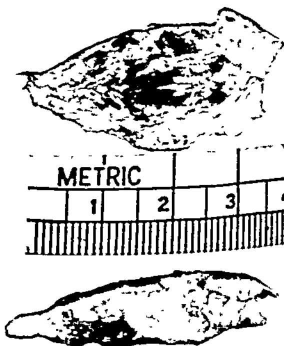


Fig. 15-44. The specimen obtained in endarterectomy of the carotid bifurcation.

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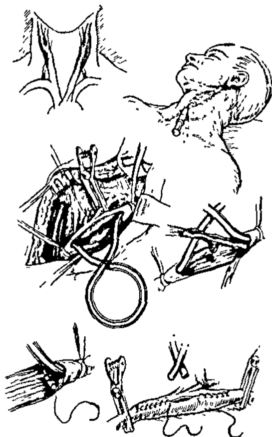


Fig. 15-45. Steps of carotid endarterectomy under local anesthesia using a temporary bypass shunt.

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was outstanding; after 1 week, this patient began to respond and he recovered completely from the episode. He has remained asymptomatic for the past 6 months.

Patients in category I are well suited for surgical intervention. Eighty per cent of these patients have remained asymptomatic following surgery; an additional 12 per cent have improved significantly.

In category II, surgical intervention is contraindicated unless operation can be performed shortly after acute occlusion occurs. The authors have seen 25 patients with complete occlusion of either the internal carotid or the vertebral artery. Eight patients of this group were operated upon. Blood flow was restored in only three: two were greatly benefited by surgery; one died from extension of thrombosis.

Patients in category III were carefully studied prior to surgery. Neurologic examination, electroencephalogram, psychometric studies, and ophthalmodynamometric readings were recorded in the majority of these patients. A remarkable response was noted in some, including significant improvement in memory, ability to concentrate, and a reversal of abnormal EEG. Six patients in a group of 16 have remained asymptomatic since surgery.

SUMMARY

Clinical features of patients with cerebral-arterial insufficiency were classified into three categories. The ideal candidate for endarterectomy is the patient with partial and segmental occlusion of the internal carotid artery and vertebral artery. Bypass graft with crimped Dacron tube is preferable in more extensive lesions of the common carotid, brachiocephalic artery, or subclavian artery. Complete occlusion of the internal carotid artery is not operable. Therefore, great emphasis should be placed on diagnosis of symptomatic arterial stenosis.

TABLE 15-15 SURGICAL RESULTS IN 146 PATIENTS WITH CEREBRAL ARTERIAL INSUFFICIENCY

	No. of patients	*Treatment, with no. of operations*	*Restoration of blood flow*	*Absence of symptoms*	*Improvement*	*Occurrence of late thrombosis*	*Death in immediate postoperative period*
Category I	122	Endarterectomies, 123 *, grafts, 10	122	98	15	2	1
Category II	8	Endarterectomies, 8	3	2	1	0	1
Category III	16	Endarterectomies, 27 †, grafts, 3	16	6	5	1	1

* Eleven patients had bilateral carotid endarterectomy.
† Thirteen patients had bilateral endarterectomy; 1 patient had both graft and endarterectomy.



I

Less common causes of cardiovascular disease[1]

NATHANIEL E. REICH

An arbitrary selection and discussion of the less common causes of cardiovascular disease must of necessity be sharply limited in order to keep within the requirements of an introductory chapter Obviously, they cannot be discussed in any great detail, nor can extremely rare or bizarre conditions be included.

NONSTRUCTURAL CARDIOVASCULAR ABNORMALITIES

Many unrelated conditions of essentially nonorganic nature can affect the cardiovascular apparatus Changes in the normal rhythm or the appearance of symptoms and signs are the most common sequelae. They do not produce appreciable structural changes, except in rare instances. However, these conditions frequently precipitate or aggravate latent or unknown heart disease They may even produce temporary exhaustion of the normal cardiac reserve A disastrous outcome is *possible in* rare instances, such as *cardiac standstill* occurring during surgical operations Electrocardiographic alterations are of vital importance in their diagnostic and prognostic evaluation. Of course, the electrocardiographic findings must be balanced with the history, physical examination, roentgenograms, blood studies, and exercise and other specific tests. The effects of work and exercise, atmospheric pressure, anesthesia and surgery, and electric shock will be discussed below.

Effect of Work and Exercise on the Heart. Although it has been shown repeatedly that strenuous training or unusual exertion extended over a long period of time may produce cardiac enlargement, this increase is distinctly of a temporary nature In instances in which heart failure has followed excessive physical strain, previously acquired heart disease usually existed. Transitory, nonfatal collapse following severe physical effort in sports or at work may be caused by orthostatic hypotension. This is due to pooling of blood in the dependent lower extremities, probably as a result of dilatation and failure of the muscular venopressor mechanism, and is frequently connected with a disturbed function of the carotid sinus receptors.

Atmospheric Changes. The cardiovascular system is profoundly affected by changes in atmospheric pressure. Characteristic syndromes are produced when individuals are subjected to an atmosphere which is markedly rarefied These alterations may be acute, e g., in sudden airplane climbs or in sudden decompression, as in the rapid return to sea level from the ocean depths, or they may be chronic, with a tendency for adaptation, as in mountain sickness In the latter, there is a close relationship

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[1] This chapter has been prepared as an introductory presentation of several disparate topics, which will be discussed in greater detail in the following chapters of this part. A few subjects (Mycotic and Parasitic Diseases) have been discussed in Part 8. On the whole, this comprehensive survey seems helpful in completing and synthesizing a score of topics which have been called "less common cardiovascular diseases." *Editor*

Of course, the electrocardiographic findings must be balanced with the history, physical examination, roentgenograms, blood studies, and exercise and other specific tests. The effects of work and exercise, atmospheric pressure, anesthesia and surgery, and electric shock will be discussed below.

Effect of Work and Exercise on the Heart. Although it has been shown repeatedly that strenuous training or unusual exertion extended over a long period of time may produce cardiac enlargement, this increase is distinctly of a temporary nature. In instances in which heart failure has followed excessive physical strain, previously acquired heart disease usually existed. Transitory, nonfatal collapse following severe physical effort in sports or at work may be caused by *orthostatic hypotension*. This is due to pooling of blood in the dependent lower extremities, probably as a result of dilatation and failure of the muscular venopressor mechanism, and is frequently connected with a disturbed function of the carotid sinus receptors.

Atmospheric Changes. The cardiovascular system is profoundly affected by changes in atmospheric pressure. Characteristic syndromes are produced when individuals are subjected to an atmosphere which is markedly rarefied. These alterations may be acute, e.g., in sudden *airplane climbs* or in *sudden decompression*, as in the rapid return to sea level from the ocean depths; or they may be chronic, with a tendency for adaptation, as in mountain sickness. In the latter, there is a close relationship

between the severity of *hypoxia* and the degree of myocardial hypertrophy. The average diameter and area of myocardial fibers increase together with the increase in heart weight. The *capillary blood supply is diminished relatively as the thickness of myocardial fibers increases.* This condition approximates that found in other forms of *hypertrophy*. Cardiovascular signs are manifested as tachycardia, cyanosis, dyspnea, palpitation, and elevated *systolic* pressure. Frank heart failure *rarely occurs* at *high altitudes*, unless there is *underlying* heart disease. Marked changes in *the electrical* activity of the heart are primarily related to the *physiological* and chemical variations induced by changes in altitude rather *than by* permanent anatomic changes

When high altitude is reached quickly, pathological changes ensue as a result of *asphyxia*. Among them are increased capillary *permeability*, *hemorrhage*, edema, and perivascular infiltration. Cerebral degenerative changes may occur, as well as hemorrhage in the myocardium, mitral valve, lungs, kidneys, and other organs. Above 18,000 ft, *collapse is generally* due to peripheral circulatory failure. A *rapid* reduction in air pressure during a rapid return *to a normal* atmospheric pressure results in a characteristic syndrome known *as compressed-air sickness (caisson disease)* *This results* from the liberation of nitrogen *bubbles in the blood stream and gives rise to air embolism.* The gas enters the left heart and death may ensue *from* hypoxia or systemic emboli

Anesthesia and Surgery. The normal cardio*vascular system* may be profoundly affected by anesthetics, as well as by *surgical* procedures In fact, the anesthetic *agent is usually* of greater importance than the operative *procedure in the* production of cardiac arrhythmias A large pro*portion of operations* are presently performed under *spinal anesthesia* Of all anesthetic procedures, this method places the *greatest* stress on the circulation, which is directly *related* to the blocking of efferent vasomotor impulses *to* arterioles, venules, and veins. The most significant changes are (1) a decrease *in blood* pressure, (2) a reduction in total *peripheral* resistance, and (3) a decrease in the *stroke* volume of the heart. Acute cardiac or circulatory emergencies may occur during the course of *inhalation anesthesia*. Induced cardiac irregularities *range in severity* from occasional extrasystoles *to ventricular fibrillation.* Minor deviations *in pulse rate,* blood pressure, or cardiac rhythm during anesthesia may assume major proportions in patients with cardiovascular disease. Although disturbances of the cardiovascular system may occur in any type of major *surgery, they* are most frequently found in association with intrathoracic operations.

Electric Shock. Electrical energy may produce deleterious effects of a serious nature on the cardiovascular apparatus. The causative factor may be generated in nature (lightning) or artificially produced (electric current). Either form may result in cardiovascular damage. The therapeutic use of *electroshock* is now limited. Besides burns and asphyxia, the *current may arrest* the heart in a firm tetanic contraction or produce ventricular fibrillation Following electroshock therapy, a great variety of arrhythmias may appear, some of which are potentially dangerous.

Effects of Drugs, Electrolytes, and Toxins on the Cardiovascular System. A surprisingly large number of diffusible drugs and other substances are capable of producing changes in the cardiovascular apparatus. Evanescent abnormalities of variable duration are frequent occurrences. Although the toxic changes, due to individual sensitivity, continued overmedication, or overexposure, are usually benign, *they may end disastrously* on rare occasions These effects also depend upon the inability of a damaged liver to detoxify them or upon *the* presence of kidney disease which prevents their normal excretion Toxic effects are exerted on the myocardium, the conduction system, or the autonomic nervous system. Transitory changes occasionally occur due to relative coronary insufficiency. This effect may be caused by focal or generalized coronary vasoconstriction or a work load on the heart increased beyond the capacity of the coronary arteries to maintain an adequate blood supply to all parts of the heart The effective agents include drugs which act upon the autonomic nervous system as they influence the cardiovascular system, drugs employed in cardiovascular therapy, drugs used in the treatment of infections, industrial toxins, and the toxic effects of diphtheria and uremia.

Stimulants *and depressants of* both the sympathetic and parasympathetic systems exert

various effects at specific sites of the autonomic nervous system. They not only increase characteristic physiological activity but may produce toxic effects on the cardiovascular system For example, *epinephrine* acts on the effector cells of the sympathetic system (see Chap 10 and Part 2, Chap. 29). The metabolic changes elicited in the heart muscle include intercellular edema, hypoxia, and diminution of creatine, phosphagen, and adenylpyrophosphoric acid The pulse rate, cardiac output, stroke volume, and left ventricular work per minute and per beat, as well as systolic pressure, are all significantly increased Electrocardiographic changes show *sinus tachycardia* and decreased voltage of the T waves in all leads In patients with coronary heart disease, there may also be depression of the S-T segment.

Toxic effects on the cardiovascular system consist of palpitation, tachycardia, and elevation of the blood pressure. Epinephrine is capable of causing myocardial hypoxia as a specific metabolic effect, *regardless of hemodynamic* conditions and regardless of the volume of coronary flow Cardiac arrhythmias may appear, and usually consist of *ventricular extrasystoles* or even *fibrillation*. In the presence of hypertensive heart disease or hyperthyroidism, there may be an increased susceptibility to the pressor effect of epinephrine The drug may also induce precordial pain in patients with coronary heart disease, but not in normal persons (except in very large doses)

A large number of drugs have as their primary function the therapeutic stimulation or depression of the cardiac structures, or the constriction or dilatation of the blood vessels These include digitalis and allied cardiac glycosides, quinidine, nitrites and other hypotensive drugs, aconitine, papaverine, mercurial diuretics, the xanthines, and procaine In addition to their specific actions, they exert toxic effects on the cardiovascular apparatus Digitalis derivatives are the most widely used of these drugs. In addition to increasing the force of systolic contraction, they also slow the heart rate by direct action on the conduction system and by vagal stimulation Toxic effects are associated with alterations in cardiac rate and rhythm and may produce almost any type of arrhythmia

Antimony and arsenical compounds, antimalarial drugs, and anthelmintics are commonly employed in various infections and infestations They are also capable of producing toxic myocardial effects (see Chap 8).

Gases and vapors, lead products, pesticides, and industrial solvents may exert toxic effects on the cardiovascular apparatus. *Carbon monoxide* produces myocardial hypoxia by its greater affinity for hemoglobin than that of oxygen. The pathological lesions are primarily vascular and consist of small hemorrhages and perivascular infiltrations with focal necrosis The heart shares in the characteristic "cherry red" staining of all organs and the skin Cardiac symptoms and ECG changes are common *Cyanides* cause asphyxial death by interfering with the respiratory ferments of tissue cells as well as by their toxic effect on the heart

While the main effect of *diphtheria* on the heart is usually due to a potent circulating toxin, direct bacterial invasion of any of the three heart layers is also possible The main toxic effect is the production of parenchymatous degeneration and necrosis and small hemorrhages in the myocardium In nonfatal cases, these areas heal with scarring which frequently involves the conduction system Heart block is most common. Sudden death may occur in overwhelming infections *Uremia* is the symptom complex of toxemia associated with *renal insufficiency*, and is due to the retention of nitrogenous and other end products of metabolism, as well as to profound electrolytic disturbances. These important but unclarified alterations occurring in the uremic state contribute to the development of so-called "uremic heart disease." The toxic effects of uremia produce organic as well as functional changes in the heart In the heart muscle of uremic persons, severe degenerative changes are frequently observed, as well as a diminished creatine concentration, similar to that which follows toxic doses of epinephrine Fibrinous pericarditis frequently occurs as a terminal event.

TUMORS OF THE HEART

The estimated ratio of primary to secondary tumors of the heart is 1:16 Primary tumors of the heart which have been reported have been identified as myxoma, fibromyxoma, sarcoma, fibroma, lipoma, rhabdomyoma, endothelioma, lymphangioma, lymphangioendothelioma, hemangioma, hemangioendothelioma, leiomyoma,

and mesothelioma. Because of their location, even benign tumors may be harmful (see Chap. 6).

Metastatic involvement of the heart may arise from any tissue within the body and arrive at the heart by hematogenous, lymphatic, or direct spread. The most common sources of the primary lesions are the trachea, breast, lung, stomach, esophagus, kidney, and pancreas. The most commonly diagnosed types have obviously been *malignant melanoma*, *primary carcinoma of the lung*, and *lymphoblastoma*.

The greatest difficulty in diagnosis lies in the fact that the major portion of the heart muscle may be invaded without producing symptoms or signs referable to the heart. The variability of the size, number, and position of the tumor masses results in a varied clinical picture. In the case of *metastatic tumors*, symptoms due to the primary lesion may overshadow those of cardiac origin The growing lesions tend to produce an ever-changing clinical picture. Cyanosis, dyspnea, variable arrhythmias, murmurs, and eventual unexplained rapid heart failure, are suggestive features. Pericardiocentesis may reveal characteristic neoplastic cells. Localized irregularities in the cardiac contours may become evident and the ECG changes may suggest the diagnosis.

MYCOTIC AND PARASITIC DISEASES OF THE HEART

Common infections of the heart of *bacterial*, *rickettsial*, and *viral* origin are discussed elsewhere (Part 8). The *mycoses* capable of involving the heart comprise a much smaller group of diseases resulting from widespread infections by pathogenic fungi Although many of these agents are world-wide in distribution, they are of the greatest significance in the tropics, where the climate and poor sanitation provide an especially favorable environment. Diagnosis usually depends upon cultural methods.

Actinomycosis was one of the first diseases recognized as being caused by a fungus About half of the cases with direct extension to the heart show clinical manifestations. Congestive heart failure is most common, but pericardial rubs and murmurs may be present Histologically, suppuration is a feature of all active lesions. The demonstration of the typical sulfur granules and the "actinomycete rosette" in the tissue or exudate is usually sufficient to establish the diagnosis *Blastomycosis* is characterized by suppuration and granulomatous lesions in any part of the body. Although the skin, lungs, and bones are usually involved, the heart and pericardium may also become affected. *Histoplasmosis* and *sporotrichosis* may also affect the heart. More recently, the increasing occurrence of *moniliasis* following the use of many antibiotics has produced a number of instances of mycotic endocarditis and interstitial myocarditis.

Many cardiac diseases of parasitic origin have become universal since World War II. Most protozoan and helminthic infections are quite insidious and chronic and may prove baffling. Recent studies of the incidence and cardiologic characteristics have increased the significance of some of the following diseases

1. Protozoan diseases which are capable of producing cardiovascular involvement: *malaria*, *American trypanosomiasis (Chagas' disease)*, and *sarcosporidiosis*.
2. Helminthic diseases: *trichinosis*, *strongyloidiasis*, *filariasis*, *schistosomiasis*, *heterophyiasis*, *cysticercosis*, and *echinococcosis*.

Hookworm and *fish tapeworm* may produce cardiac dilatation and murmurs because of severe anemia. The parasite *Trypanosoma cruzi* exhibits a distinct preference for the myocardium in the chronic form of the disease It is primarily a disease of young adults. The clinical picture is one of congestive failure which persists for months or years, usually proves resistant to treatment, and finally terminates in death. Myocarditis is the most important complication of *trichinosis* It may appear as early as the second week and may severely affect the myocardium by a direct invasion of the larvae, this results in marked parenchymatous degeneration Advanced myocardial damage may eventually produce the clinical picture of cardiac insufficiency. Species of *Schistosoma* derived from infected snails may involve the lungs with resultant chronic cor pulmonale, or the ova may directly invade the myocardium. Cardiac manifestations are due to localized inflammatory reactions of the foreign-body type. Later, the ova become encapsulated by connective-tissue proliferation

which may then become calcified *Echinococcus* may infest the heart and produce cardiac cysts (see Part 8, Chap 10).

TRAUMA OF THE HEART

The heart may be traumatized by indirect or nonpenetrating direct injuries as well as by penetrating agents (see Chap. 7). *Contusion of the heart* (*contusio cordis*) may occur despite the fact that this vital organ is well protected by the bony thoracic cage and is a mobile structure which can move with the force of the blow. It is likely to follow *steering wheel injuries* and serious falls Contusio cordis mainly results in damage to the myocardium Small hemorrhages are due to rupture of the smaller vessels Actual *rupture of the heart muscle* may occur to a lesser or greater degree Constant oozing results in compression of the heart (cardiac tamponade). *Tamponade* may also be due to pericardial bleeding without actual rupture of the myocardium Softening and fibrosis of a contused area occasionally give rise to the formation of a localized aneurysm

Acute or chronic tamponade is usually the main feature of *penetrating injuries* Most authors disclaim the influence of *trauma* in the causation of coronary thrombosis with myocardial infarction unless there is a direct injury to these vessels. Cardiac involvement may present symptoms of precordial pain, cyanosis, and dyspnea. Arrhythmias or left ventricular failure may also occur. A rapidly changing electrocardiographic picture is significant Compression of the heart produces a characteristic syndrome (tamponade). The increasing pericardial pressure compresses the large veins entering the heart with a resultant decline in arterial pressure and a rise in venous pressure As the condition progresses, the pulse pressure fails, the pulse rate increases, and symptoms of cardiac failure intervene

CALCIFICATION OF THE MYOCARDIUM

Calcification of the myocardium may be considered as of primary origin when the initial pathologic change exists in the myocardium, in contradistinction to secondary types which depend upon mobilization and deposition of calcium in the myocardium as a result of extracardiac causes. *Primary calcification* of the myocardium may occur shortly after birth as a result of either early degenerative or inflammatory processes. Myocardial lesions due to infarction, degenerative disease, or various types of myocarditis, may leave calcium compounds deposited in the affected areas This calcification is considered a late healing stage and occurs most frequently following myocardial infarction. Since circulation is absent in necrotic areas, a slow diffusion of calcium salts takes place from the blood and lymph channels of the surrounding tissues This condition has also been termed "primary massive calcification of the myocardium" Since it is most frequently caused by coronary occlusion, it is most commonly found in the left ventricle Calcification may also occur in the organized thrombus contained within a ventricular aneurysm, as well as in cases of adhesive and constrictive pericarditis (Fig 16-1). Metastatic or *secondary calcification* of the myocardium may be seen in hyperparathyroidism, hypervitaminosis D, and diseases associated with severe osteoporosis, such as osteomalacia and osteitis fibrosis cystica. In these instances, the calcium is removed from the bones and deposited in the heart and other tissues. The calcified areas may be readily visible in motion under fluoroscopic examination.

AMYLOIDOSIS

Amyloidosis is an uncommon degenerative process in which progressive cardiac involvement may be followed by heart failure (see Chap. 5) Amyloid is a foreign material which is produced and deposited in various body tissues The substance is a glycoprotein consisting of two protein and one polysaccharide fractions It is believed either that it is a product of the combination of a component of serum globulin and a fixed component of the vascular system, or that the presence of hyperglobulinemia results in the deposition of excess globulin in the tissues *Primary systemic amyloidosis* is a form of the disease in which no preexisting illness is present and in which the material is often deposited prominently in the heart and other mesodermal structures *Secondary amyloidosis* is associated with preexisting chronic diseases which include syphilis, chronic suppuration, chronic severe anemia. chronic

arthritis, tuberculosis, and malignancy Localized amyloid deposits may be found. Occasionally, amyloidosis is found in association with multiple myeloma. The most remarkable feature of the primary type is that the greatest concentration of amyloid is distributed throughout the myocardium. Atrial and ventricular walls may be thickened, and appear hard, grayish-tan, waxy or translucent, glossy and stiff, or leathery in instances in which amyloid is diffusely distributed Imprisoned myocardial fibers thus may (1) be compressed, (2) degenerate, (3) become necrotic, and (4) finally disappear leaving empty amyloid rings These pericellular deposits may be continuous with amyloid in the blood vessels of the myocardium. Amyloid may also be deposited in the other heart layers and valves and the coronary and pulmonary arteries. Thus, cardiac failure, coronary insufficiency, or valvular deformities may predominate in the clinical picture. Involvement of the lungs and mediastinum may contribute to the cardiac failure by the development of chronic cor pulmonale. Biopsy and Congo-red test are diagnostic. *Low voltage* of all complexes is a prominent electrocardiographic feature.

SARCOIDOSIS

Sarcoidosis is a chronic, benign, granulomatous process of unknown cause mainly involving the lymphatic tissue It may occur at any age but is most frequent between the ages of 15 and 40 years. There is no sex predominance, but Negroes appear to be affected more frequently than Caucasians. Involvement of the myocardium may be due to a focal or diffuse *granulomatous myocarditis* associated with cardiac hypertrophy. Electrocardiographic changes which have been noted include inverted T waves suggestive of myocardial damage, and arrhythmias. Findings are present which also suggest pericardial involvement. *Chronic cor pulmonale* secondary to marked pulmonary sarcoidosis results in signs of right



Fig 16-1. Calcification of cardiac structures A Calcification of mitral ring (2) and aortic leaflet (1), with movements clearly visible on fluoroscopy B Concretio cordis Complete envelopment of the heart. C Concretio cordis Localized envelopment of the heart Angiocardiograms (3-sec film) outlining left atrial wall, which is completely circumscribed by localized calcification of wall (arrows) compressing the pulmonary veins as they enter this chamber.

heart failure and death. Hyperglobinemia, hypocalcemia, negative tuberculin test, skin biopsy, and bony changes are important laboratory data which aid in diagnosis.

UNCOMMON DISEASES OF THE ENDOCARDIUM

Endocardial disease is usually an endocarditis mainly affecting the valves The major etiologic types are discussed in detail elsewhere (Part 8). Besides the common rheumatic fever, bacterial endocarditis, and syphilitic infection, tuberculosis may also affect the valves in rare instances. Bacterial endocarditis may extend to the mural endocardium The thrombotic lesions are sterile in *Libman-Sacks disease* and in other collagen diseases which affect the valves. The occurrence of *fetal endocarditis* has never been established since unequivocal evidence of inflammation is seldom found. It is probably a developmental defect. *Endocardial pockets* resemble valve cusps in form They are usually found on the left side of the interventricular septum and are due to the marked regurgitation of blood resulting from aortic insufficiency. A similar pocket may be produced by the continuous pressure of blood exerted upon the entrance of an aortic stenosis

Fibroelastosis. Considerable attention has been given to the occasional finding of a glistening, white or yellow thickening of the endocardium with or without valvular deformity This fibroelastic tissue has been attributed to inflammatory residuals or developmental defect (see Chap. 12). Because of associated congenital defects and the absence of true earmarks of inflammation, the developmental idea is more acceptable in many instances. Endocardial thickening interferes with the emptying of intraluminal vessels into the ventricles The resulting anoxemia eventually leads to myocardial damage and failure.

In addition to the primary congenital type, an acquired type may also occur Diffuse or circumscribed lesions may be due to a variety of causes. Endocardial thickening may occur following a number of primary lesions of the myocardium. This results from either the healed endocardial element of myocardial infarction or as the end stage of an organized mural thrombus Elastic tissue is absent in such cases. Marked hypertension has never been proved as a factor in children Congenital anomalies of the origin of the coronary arteries usually cause *endocardial fibrosis* as well as myocardial hypertrophy. Circumscribed sclerotic lesions are the seat of old nonrheumatic endocarditic lesions, since the valves are not involved. When the left ventricular wall is dilated and hypertrophied, it resembles that of cases reported as "idiopathic hypertrophy of the heart." The left ventricle is small in the contracted or constrictive type of endocardial sclerosis. This prevents adequate diastolic expansion and eventually gives rise to right ventricular hypertrophy.

UNCOMMON CAUSES OF PERICARDIAL DISEASE

Congenital Deficiency. A defect or total absence of the pericardium has been attributed to a premature atrophy of the left duct of Cuvier owing to an anomaly of the circulation of the great venous trunks. In turn, the arrested development of the primary ridge results in a localized defect of the pleuropericardial septum, which normally develops during the fifth week of prenatal life. This is not incompatible with normal cardiac activity since the function of a frictionless serous sac may be replaced by the pleural cavity. There are no symptoms in uncomplicated cases Roentgenograms in the right and left lateral recumbent positions may reveal wide excursions of the heart.

Coelomic Cyst. Coelomic cyst of the pericardium is of mesodermal origin and of simple anatomic structure. The pericardium arises from a series of disconnected lacunae in the mesenchyme which appear early in embryonic life The failure of a lacuna to merge with the others in the formation of a pericardial coelom, and its progressive enlargement, give rise to a cyst connected or adjacent to the pericardium.

Pneumopericardium. *Pneumopericardium* signifies the presence of gas within the pericardial sac, this is due to a variety of causes. The gas may prove irritating, giving rise to [illegible]

[illegible] infection of the pericardium is usually the cause In lesions causing rupture of the esophagus, examination reveals pericardial tympany and distant heart sounds with

splashing or churning noises due to the presence of liquid and air. Roentgenograms and aspiration reveal specific changes.

Chylopericardium. True *chylopericardium* does occur, and pseudochylous fluids may be aspirated from the pericardial sac following indirect or direct trauma to the thoracic duct or due to neoplastic or tuberculous invasion of the duct. Aspiration of a milky fluid is characteristic. Pseudochylous fluid does not contain fat, but it has a milky appearance due to the presence of fine albuminous particles.

Acute Nonspecific (Idiopathic) Pericarditis. Acute nonspecific pericarditis pursues a relatively benign clinical course without evidence of any associated or primary disease. (See Part 8, Chap. 3.) Recognition of these cases is highly desirable since their differentiation from other types of pericarditis and myocardial infarction is of great importance. Although the causative factor remains obscure, it is a frequent sequela to upper respiratory infections The possibility that the disease represents an antigen-antibody reaction with sensitization of the pericardium and subsequent inflammatory reaction on exposure to bacterial antigen cannot be excluded. A history of recurrent attacks may be obtained in a fair number of cases. This susceptibility to reinfection is similar to that seen in rheumatic fever. The involved areas of the pericardial sac lose their normal glistening appearance and become dull and opaque. Fibrin deposits may advance to the stage where the heart surface has a shaggy appearance ("bread and butter" type). The fibrinous character of the exudate diminishes as the fibrinous effusion appears in variable amounts. The diagnosis rests upon the history of upper respiratory infection, or unexplained fever and other transitory evidence of mild infection Severe chest pain, dyspnea, fever, and pericardial friction rub occur Paracentesis reveals fluid with no bacterial content. Roentgenograms and electrocardiograms are highly distinctive. Elevation of RS-T segments and peaked T waves are characteristic.

UNCOMMON DISEASES OF THE CORONARY ARTERIES

A large number of neglected conditions affecting the coronary arteries may occur, some of which are of increasing clinical importance because they are observed more often.

Most anomalies of the coronary circulation consist of a displacement of the origin of one or the other of the main coronary arteries due to a slightly abnormal location or absence of a primordial vascular bud There is a frequent association with other congenital anomalies, such as transposition of the great vessels Thus, a single coronary artery may occur or the left coronary artery may originate from the pulmonary artery. Subendocardial fibroelastosis has been attributed to the resultant anoxemia. Anomalies of secondary and tertiary branches are also possible. For example, the left circumflex artery may arise from the right coronary artery. Supernumerary coronary arteries and coronary arteriovenous fistulas have also been reported. Congenital necrosis of the media of coronary arteries has also been described (Gruenwald).

Specific infections and parasitic diseases, such as syphilis (see Part 9) and malaria (see Part 8), are considered elsewhere.

Aneurysms of the coronary arteries are usually of congenital or embolic-mycotic origin Arteriosclerosis, syphilis, and collagen diseases have also been at fault on occasion.

Emboli may interfere with the coronary circulation They may be due to air, fat, bacteria, a neoplasm, or a blood clot.

BLOOD DYSCRASIAS AND HEART DISEASE

Disorders affecting individual blood elements may produce structural and physiological changes of the heart and blood vessels. Therefore, specific diseases affecting the red and white blood cells and the platelets will be considered. (See also Chap. 11.)

Diseases of the Red Cells. Several important disorders of the red blood cell may affect the cardiovascular apparatus if severe or prolonged in nature.

SECONDARY ANEMIA. Hypoxia due to anemia produces effects which are similar to those seen in diseases which interfere with respiration, coronary insufficiency, carbon monoxide or cyanide poisoning, or excessive methemoglobin formation. In the presence of advanced and chronic forms of anemia, fatty degenerative changes occur; these may affect myocardial efficiency to variable degrees. Cardiac dilatation and hypertrophy also occur. The role of anemia in the production of *interarterial*

coronary anastomoses is of considerable importance They occur in only 10 per cent of normal hearts from patients with normal hemoglobin levels On the other hand, anastomoses are present in 35 per cent of the hearts of patients with antecedent anemia and with hemoglobin values lower than 70 per cent. An adequate oxygen supply to the tissues is maintained in chronic severe anemia by an increased cardiac output, an increased velocity of blood flow, and a relatively more complete extraction of oxygen from the blood as it passes through the capillaries. A decrease in peripheral resistance is related to the increased blood flow. The blood volume is generally slightly reduced but the plasma volume is normal The deviations from the normal values vary, but they are generally distinct when the hemoglobin values are less than 50 per cent.

Cardiac manifestations include palpitation and dyspnea on exertion, tachycardia, cardiac enlargement, murmurs, and electrocardiographic changes The arterial pressure is frequently lowered while the *venous pressure* is generally within normal limits Precordial pain and congestive failure occur in some patients and disappear as the anemia is alleviated In fact, *precordial pain* may be the predominating complaint in many patients suffering from severe chronic anemia. It persists until the anemia is relieved The problem of differentiating the exertional dyspnea, edema, and hepatomegaly associated with severe anemia, from those associated with heart failure due to coronary disease, frequently presents itself Diagnostic aid is derived from the fact that, in anemia, there is neither venous engorgement nor orthopnea.

In addition to the characteristic hematologic findings, there is an increased cardiac output which occurs as a compensatory mechanism Anemia produces a shortened circulation time and tends to decrease blood viscosity, vascular resistance, and blood pressure. The electrocardiogram reveals a tendency to *low voltage* of the QRS complex, isoelectric or inverted T wave, and S-T depression. These changes disappear if the anemia is corrected The enlargement of all heart chambers also decreases with appropriate measures

SICKLE-CELL ANEMIA. This disease is chronic, hereditary, familial, and almost exclusively confined to Negroes It is frequently associated with myocardial involvement and chronic cardiac failure. Cardiac changes are due to thrombosis of the small vessels of the heart and lungs, as well as to the anoxemic effects of the marked anemia. An asymptomatic sickle-cell trait (*sicklemia*) is found in about 8 per cent of all Negroes A small proportion (6 to 8 per cent) of them develops a marked anemia and characteristic symptoms (sickle-cell anemia). The anemia, systemic thromboses, fever, jaundice, and cardiac findings may be confused with the signs of acute rheumatic fever or bacterial endocarditis.

The abnormal shape of the erythrocytes is responsible for the stasis of blood flow in the capillaries; this results in thrombosis, infarction, necrosis, and hemorrhage. Secondary peripheral vasospasm also aids in this process. Degenerative changes are enhanced by the anemic phase. The heart becomes dilated and hypertrophied with a pale myocardium. The cardiac weight ranges between 225 and 440 Gm. Microscopic changes include interstitial edema, myocardial degeneration, vacuolated sarcoplasm, Zenker's degeneration, and interstitial infiltration by white cells. An extreme tortuousness of the blood vessels develops, and the occlusive involvement of the small pulmonary arteries may result in *chronic cor pulmonale*.

The symptoms include weakness, fatigability, and pallor. The signs are mainly due to vascular occlusions with infarctions of the spleen, brain, heart, and kidneys Therefore, signs referable to any of these organs may be found. Sinus arrhythmia and tachycardia are frequent. There is a diffuse heart enlargement A *diastolic tap* may be felt over the pulmonic area, and a *systolic thrill* is frequently present over the precordium. A systolic murmur of variable intensity may be loud enough to obscure the 1st apical sound, or a presystolic murmur may blend with the 1st sound. These murmurs are frequently mistaken for those due to rheumatic or congenital heart disease. Signs of right-sided failure (*cor pulmonale*) may eventually appear Roentgenograms reveal a globular enlargement of the heart and a prominence of the pulmonary conus. Bone changes are diagnostic. Electrocardiographic changes may occur, due to thrombosis of small coronary vessels If the injury has not been too extensive, reversal of the process may take place.

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Disorders affecting individual blood ments may produce structural and physio cal changes of the heart and blood ves Therefore, specific diseases affecting the and white blood cells and the platelets be considered. (See also Chap. 11.)

Diseases of the Red Cells. Several impor disorders of the red blood cell may affect cardiovascular apparatus if severe or prolon in nature.

SECONDARY ANEMIA. Hypoxia due to an produces effects which are similar to t seen in diseases which interfere with res tion, coronary insufficiency, carbon mono or cyanide poisoning, or excessive methe globin formation. In the presence of adva and chronic forms of anemia, fatty degen tive changes occur; these may affect myo dial efficiency to variable degrees Car dilatation and hypertrophy also occur. The

and white or gray, but may become hemorrhagic In general, hemorrhage is more common in the acute form and is associated with thrombocytopenia Fatty degeneration may also occur as a result of the accompanying anemia. This is the probable cause of progressive heart failure.

Pericardial involvement frequently gives rise to a hemorrhagic fluid, from which the characteristic cells may be centrifuged and identified after staining Myocardial invasion may affect the conduction system, as well as the myocardium. The resultant clinical and electrocardiographic picture may thus assume many forms

The diagnosis of leukemic infiltration of the heart may be suspected when the hematologic diagnosis has been established and there are cardiac symptoms and signs with progressive electrocardiographic changes. Fluoroscopy and kymography may reveal localized areas of absent pulsations in affected areas.

Diseases of the Platelets. The presence of an increased or decreased number of platelets in the circulating blood may affect the cardiovascular apparatus. The increased production of platelets with an instability of suspension appears to be the pathological process occurring in an unusual disorder known as *essential thrombophilia* This situation favors widespread thrombus formation Thus, the vessels of the extremities, heart, brain, and kidneys may become involved The diagnosis may be established by the elevated platelet count, plasma coagulability studies, and increased plasma globulin fraction in the presence of multiple thrombosis without evidence of underlying vascular damage

A quantitative or qualitative deficiency of the platelets is associated with a tendency to hemorrhage. Purpura is due to a significant reduction in the number of platelets and is known as *thrombocytopenic purpura* Many blood disorders may be associated with this condition and include various anemias and leukemias, as well as numerous infectious and certain splenic disorders The effects on the cardiovascular apparatus are not only those due to bleeding into the myocardium and around blood vessels, but also those due to the secondary effects of the chronic blood loss Diagnostic studies include (1) a platelet count, (2) bleeding time, (3) clot retraction, and (4) a tourniquet test.

METABOLIC DISORDERS AND THEIR EFFECTS ON THE CARDIOVASCULAR SYSTEM

The cardiovascular system may be affected by certain metabolic disorders. In most instances, specific endocrine dysfunctions are involved; in some cases, enzyme systems are at fault. Hormones elaborated by the endocrine system act by augmenting or inhibiting the activity of specific enzyme systems Overactivity or underactivity of the glands may result in cardiopathies that are more or less characteristic Many chemical events require the presence of highly specialized protein catalysts known as *enzyme systems*. The effect of hormones is discussed in Part 2, Chap 29. Disorders of endocrine glands are discussed in Chap 10.

The Thyroid Gland. THYROTOXIC HEART DISEASE. The occurrence of cardiovascular involvement during hyperthyroidism is well recognized. The disease occurs most frequently during the second and third decades of life The incidence in women is much higher, being in the ratio of 5:1. However, since men are more severely affected, a relatively higher percentage of cardiac involvement is found in this group

Excessive secretion of thyroxin results in increased metabolic function which obviously makes greater demands upon the cardiovascular system Increased oxygen consumption is associated with an elevated cardiac output Persistent overactivity results in variable degrees of hypertrophy of the heart muscle. Eventually, the cardiac reserve becomes completely exhausted and congestive heart failure ensues The direct toxic effect of thyroxin on the heart muscle may add to the strain on the myocardium, as well as cause intractable atrial fibrillation It becomes evident much sooner in the presence of other underlying heart disease Myocardial edema, necrosis, and fibrosis, due to direct thyrotoxic effects, have been described but their existence is not accepted by all investigators.

The course of thyrotoxic heart disease is variable depending on the age of the patient and severity and duration of the intoxication

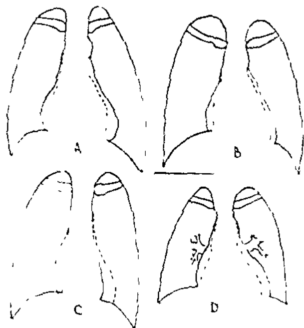


Fig. 16-2. The effects of *specific therapy on the* heart size. A. *Myxedema* showing generalized cardiac enlargement. Dotted lines indicate reduction in size after 2 months of treatment with thyroid extract. B. Thyrotoxicosis with generalized increase in heart size. Dotted lines show decreased size as *metabolic* rate is improved after 4 months of therapy with propylthiouracil C. Addison's disease revealing marked decrease in the cardiac silhouette. *Dotted lines show* increase in size one month following treatment with *adrenocortical extract* and sodium chloride. D Pernicious anemia. Note *generalized* cardiac enlargement and prominence of hilar markings After 2 months of intensive specific therapy, there is *return to normal* (dotted lines).

Depression of the R-T junction and flat or *inverted T waves* are commonly noted

PERNICIOUS ANEMIA Pernicious anemia is a chronic disease which is characterized by an insidious onset, macrocytic hyperchromic anemia, achylia gastrica, and disturbances of the *gastrointestinal, nervous,* and cardiovascular systems.

The heart is dilated and hypertrophied, frequently weighing up to 600 Gm The muscle layers appear pale, with microscopic evidence of diffuse fatty degeneration This produces yellow streaks at the venous end of the capillaries. This has been referred to as *tiger-lily heart.* Evidence of congestive failure is found terminally.

The symptoms referable to the circulatory system may be so pronounced as to lead to a mistaken diagnosis of primary cardiovascular disease. Symptoms include dyspnea, dependent edema, and precordial pain. Weakness, fatigability, palpitation, basal rales, and even ascites, may occur. Signs include a systolic murmur over the apical, pulmonic, or aortic areas, or *a diffuse systolic murmur* over the entire precordium. A *diastolic murmur* occasionally heard over the aortic area is attributed to dilatation of the aortic ring. Hypotension, premature beats, and tachycardia are common. Congestive failure may eventually appear.

The hemogram is diagnostic. Absence of free gastric acid following histamine injection is characteristic. The circulation time may be shortened. The electrocardiogram reveals S-T depression, flattening of T waves, and low voltage of the QRS complex in the severe forms. Roentgenograms reveal diffuse cardiac enlargement during the advanced stage of the disease *(Fig. 16-2D)*.

POLYCYTHEMIA. In both primary and secondary polycythemia, there is an increased viscosity of the blood and an increased blood volume. Cardiovascular involvement is common Although hypertrophy and dilatation are noted, the vascular manifestations are of greater significance since multiple thromboses of the arteries and veins are frequently observed. The coronary vessels may thus become involved, giving rise to a clinical and electrocardiographic picture characteristic of coronary occlusion Cerebral and other vascular thromboses and hemorrhage have also been observed. Hypertensive and arteriosclerotic changes are generally considered to be coincidental The myocardium presents a dark-red appearance.

Diseases of the White Cells: Leukemias. Leukemic infiltrations of the heart commonly occur in about one-third of all cases of lymphatic or myeloid leukemia. It was originally held that all heteroplastic leukemic nodules represent metastatic growths of embolic cells. The engorgement of myocardial capillaries with leukemic cells, frequently observed, seems to support *this view*

Besides affecting the mediastinal structures, which can indirectly affect the heart, leukemic infiltrations may invade the cardiac tissues directly These areas are not sharply demarcated, as are *most primary* and secondary tumors. Less *frequently, they* may have a nodular appearance. They are generally firm

bones (osteitis fibrosa cystica). Increased excretion of calcium phosphate results in the precipitation of renal calculi. Pyelonephritis is a frequent complication and a significant number of patients develop hypertension or renal insufficiency. The arteriovenous effect of cystic disease of the bones and *calcification of the myocardium and arteries* may also develop. The electrocardiogram reveals an abnormally abbreviated electrical systole (*short Q-T*). This finding is not specific since it also occurs with digitalis. However, the S-T segments and T waves are not depressed in hyperparathyroidism

HYPOPARATHYROIDISM Decreased secretion of parathormone may occur as the result of cystic degeneration, atrophy, or inflammation of the parathyroid glands, or of accidental removal at the time of thyroidectomy This results in a reduction in serum calcium and signs of neuromuscular hyperexcitability, such as painful spasms The most characteristic electrocardiographic change is *prolongation of the Q-T interval*. This change may also be found when the serum calcium is lowered in other disease processes, also in heart strain and myocardial ischemia

The Pituitary Gland. ACROMEGALY AND GIGANTISM Cardiac enlargement is found in association with acromegaly but it is not yet definite whether this is a feature characteristic of the generalized splanchnomegaly Heart weights have been found to average 450 Gm and may exceed 1,200 Gm Microscopy shows that the increased bulk is due to hypertrophy of the individual fibers of muscle tissue with marked lacy interstitial fibrosis. Cardiac failure and death occur in about one-fourth of the cases The occurrence of peripheral circulatory disturbances is probably due to dysfunction of the autonomic nervous system Hypertension is frequently observed but is due to concomitant hyperfunction of the basophilic portion of the gland

BASOPHILISM A basophilic adenoma of the pituitary gland is most frequently found in patients with Cushing's syndrome Occasionally, an adenoma of the adrenal cortex or a carcinoma of the thymus is at fault The clinical picture reveals painful adiposity confined to the face (moon face), neck, and trunk Kyphosis, sexual dystrophy, hypertrichosis in females, a dusky plethoric appearance associated with polycythemia, purple abdominal striae, and variable pains and fatigability, are typical findings. Hypertension is a common finding and results in hypertrophy and dilatation of the heart, arteriolar nephrosclerosis, and thickening of the arterioles in all organs of the body.

The Adrenal Glands. HYPERFUNCTION OF THE ADRENAL CORTEX Hyperfunctioning lesions of the adrenal cortex produce a variety of clinical syndromes, but only *Cushing's syndrome* falls within the scope of this text. It may be caused by a basophilic adenoma of the pituitary or by a primary hyperplasia or tumor of the adrenal cortex. An overproduction of the active adrenal compound desoxycorticosterone results in salt and water retention, edema, hypertension, and eventually congestive heart failure. The urinary 17-ketosteroids are markedly elevated, and hypochloremic alkalosis may be encountered.

HYPOFUNCTION OF THE ADRENAL CORTEX: ADDISON'S DISEASE A destructive lesion of the adrenal cortex is characterized by asthenia, pigmentation of skin and mucous membranes, gastrointestinal and nervous disturbances, and *hypotension* Tuberculosis, cysts, primary atrophy, or malignant destruction are the most important pathogenetic factors Hormonal insufficiency is reflected in increased blood levels of cholesterol, nonprotein nitrogen, and potassium, and in decreases in chloride, sodium, glucose, and hydrogen-ion concentration Excessive loss of water through the kidneys results in a negative water balance and a loss of threshold substances in the urine. The subsequent shifts of water and electrolytes from the tissues to the blood accounts for the alterations in the blood constituents. In a significant number of patients, the heart is small both in volume and weight (Fig. 16-3C), and there is an increase in the hemofuscin pigmentation of the myocardium Marked hypotension and myocardial weakness occur The electrocardiogram reveals *low voltage* of QRS complexes and T waves. Analysis of the serum reveals low sodium and chloride, and high potassium levels The ACTH test shows a decrease in circulating eosinophils

HYPERFUNCTION OF THE ADRENAL MEDULLA: PHEOCHROMOCYTOMA. Pheochromocytoma (paraganglioma) is a chromaffin tumor arising either in the adrenal medulla or in chromaffin

Palpitation and dyspnea are the first important symptoms. Vague precordial pain of a paroxysmal nature is common. Forceful pulsations of the precordium and of the large arteries are easily palpated and may be visualized. A *bruit* heard over the inferior poles of the thyroid gland is due to the greatly increased blood supply of this gland. A functional systolic murmur of harsh character may be heard to the left of the sternum. It is usually attributed to the increased pulmonary circulation with dilatation of the pulmonary artery. Wide pulse pressure is due to moderate elevation of the systolic pressure and slight decrease in the diastolic pressure. The systolic pressure rarely exceeds 160 mm Hg. Occasionally, there may be confusion with aortic insufficiency. Cardiac enlargement occurs eventually in most cases (Fig. 16-2B). Common disturbances of rate and rhythm are sinus tachycardia and atrial fibrillation, but extrasystoles, atrial flutter, and supranodal tachycardia are not unusual

Fluoroscopy reveals markedly increased activity of the cardiac contractions The outflow tract of the left ventricle may show the earliest evidence of cardiac hypertrophy and there is prominence of the pulmonary artery. The ECG is not diagnostic. Besides possible arrhythmias, low or inverted T waves may be found, especially in lead II. Left ventricular strain patterns become evident in long-standing cases. Tracer tests with radioactive iodine (I^{131}) are considered diagnostic for hyperthyroidism The protein-bound iodine level and basal metabolic rate determination are not quite as accurate, but are more readily available Circulation times are markedly decreased

MYXEDEMATOUS HEART DISEASE. Cardiac dysfunction due to underactivity of the thyroid gland occurs in approximately three-fourths of untreated cases. The disease occurs at any age and has no sex predominance

The initiating causes of the hypothyroid state are (1) insufficient thyroid activity associated with thyroglandular atrophy, (2) pituitary dysfunction, (3) too radical thyroid extirpation for thyrotoxicosis, (4) overtreatment with antithyroid compounds, or (5) excessive use of radioactive iodine for coronary heart disease or myocardial insufficiency As a result, the heart undergoes enlargement, partly because of the myxedematous state of the cardiac structures and partly because of hydropericardium and cardiac dilatation (Fig 16-2A). The musculature, which appears translucent and light red, may dilate to such an extent that a functional insufficiency of the atrioventricular valves results. Although the microscopic changes are not specific, an edematous material is usually found between the muscle fibers. The frequent association of premature arteriosclerosis, especially of the coronary arteries, is probably due to an increase in blood cholesterol level which is secondary to the thyroid dysfunction

Cardiac symptoms may not become evident unless sudden demands are made upon the decreased cardiac reserve. Dyspnea becomes more pronounced as congestive failure progresses. Precordial pain is due to the frequent association of coronary artery sclerosis However, it may also follow thyroid therapy since the sudden increase in metabolism may result in relative coronary insufficiency. Bradycardia is a constant finding Cardiac enlargement is due to increased bulk as well as to dilatation although hydropericardium may also contribute. Weakness of the heart sounds may be evident, because of sluggish heart action Relative mitral and tricuspid insufficiency may appear as a result of cardiac dilatation.

Roentgenograms show a generalized increase in heart size. Fluoroscopy, roentgen kymography, and electrokymography show markedly decreased pulsations despite the increased heart size. The therapeutic response to specific therapy is striking and diagnostic within a few weeks. Characteristic electrocardiograms show sinus bradycardia, low voltage of the QRS complexes, and flat or inverted T waves in the standard and chest leads. There may be varying degrees of AV block These findings disappear with appropriate therapy Other studies reveal decreased cardiac output and prolonged circulation time. Blood cholesterol levels are high while protein-bound iodine levels are diminished. The glucose tolerance curve is flat. Basal metabolic rate is usually below 30 per cent of normal.

The Parathyroid Glands. HYPERPARATHYROIDISM The parathyroid glands secrete a hormone (parathormone) which mobilizes calcium and maintains a normal serum calcium level Hyperplasia or tumor of these glands produces an increase in hormonal secretion which results in calcium mobilization and decalcification of

heart and other organs may suffer deleterious effects. *Insulin hypoglycemia* is due to excessive administration of insulin. When hypoglycemic levels are reached, there is a release of epinephrine and norepinephrine which drives the blood sugar levels above the original peak of hyperglycemia. Hypoglycemic attacks are not likely to occur during the management of young, markedly advanced, or sick diabetic subjects. Attacks are especially deleterious in diabetic patients with congestive failure, acute coronary thrombosis, or severe angina pectoris *Spontaneous hypoglycemia* may be caused by diseases of the endocrine system, such as hyperinsulinism due to hyperplasia or tumors of the islets of Langerhans, Addison's disease, Simmonds' cachexia, or hypothyroidism. Extensive liver disease, such as marked metastatic involvement, cirrhosis, infectious hepatitis, and poisoning, may also be at fault. Disturbances of the nervous system, malnutrition, diarrhea, and renal glycosuria are rare causes

Although neurologic symptoms predominate during a hypoglycemic attack, the cardiovascular system is also involved Hypoglycemia is accompanied by increased cardiac work and may have serious effects on a previously damaged heart Cardiac arrhythmias, hypertensive encephalopathy and coronary heart disease are known to occur. During attacks, elevation of S-T segments, and various arrhythmias are noted in the electrocardiogram. These changes are reversible with therapy.

Glycogen Storage Disease (von Gierke's Disease). Glycogen storage disease is due to a developmental defect involving the enzyme systems necessary for the transformation of glycogen to dextrose and vice versa Since islet hyperplasia is frequently found, there is a possibility that it is a response to the increased demand for insulin Most children with the disease die during the first year of life Although the liver, kidney, and reticuloendothelial system are the main sites for the pathological storage of glycogen, histochemical methods and chemical analysis reveal that the heart has been affected. The heart is moderately enlarged due to the abnormal glycogen storage. Myocardial fibers appear hypertrophied and vacuolized by tiny glycogen deposits The latter appear as large empty spaces which crowd the nuclei toward the periphery of the cells. These deposits cause up to a five-fold increase in the size of the individual myocardial fibers. Because of the diffuse involvement, the electrocardiographic picture is one of combined heart strain When the heart is predominantly involved, cyanosis and dyspnea or unexpected death is the rule

Laboratory tests reveal hypoglycemia and ketosis in the fasting condition. Absence of hyperglycemic response to epinephrine and an abnormal glucose tolerance curve unaccompanied by glycosuria are also noted, as well as decreased glycogenolysis. Normal diastase activity and hypercholesterolemia are found.

Hemochromatosis. Hemochromatosis (*bronze diabetes*) is characterized by the excessive deposition of hemosiderin and hemofuscin in various organs and in the skin. A disordered metabolism of iron in the cytochrome system provides the most plausible explanation. Most of the cases occur in persons more than 35 years old and men predominate in a ratio of 20:1 The pigment deposits produce fibrotic reactions in the liver (portal cirrhosis) and in the pancreas (bronze diabetes) Hence, death occurs as a result of the complications of portal hypertension or diabetes, or following intercurrent infection The average duration of life following diagnosis is 18 months.

French investigators considered the cardiac features so important as to name the disease "syndrome endocrino-hepato-cardiaque." The possible relationship of heart failure to profound endocrine and biochemical changes, such as adrenocortical insufficiency or hypopituitarism, requires further investigation. Myocardial changes include extensive replacement fibrosis, myocardial atrophy, vacuolization, and fatty degeneration Chemical tests reveal an increase in recoverable iron in the myocardium. When pigment deposits in the myocardium become severe enough to produce cellular degeneration, function is interfered with and heart failure may result. There appears to be no correlation between the appearance of failure and the age of onset or duration of disease, the severity or duration of cirrhosis and diabetes, and the occasional presence of hypopituitarism Neither is there any correlation between pathological changes and the abnormalities of cardiac function The latter are manifested by arrhythmias (supraventricular paroxysmal tachycardia, atrial fibrillation and flutter, heart block, and frequent extrasystoles).

tissue located elsewhere in the body. The characteristic clinical picture develops following the irregular release of significant amounts of epinephrine. Paroxysmal attacks of *hypertension* may last from seconds to hours. Palpitation, precordial distress, tachycardia, headache, anxiety, tremulousness, vomiting, glycosuria, and vasomotor phenomena may occur. The systolic pressure usually exceeds 200 mm Hg. When hypertensive attacks are frequent or sustained, cardiac enlargement is almost always present. Massage over the adrenals, bending, or surgical manipulation of the adrenals, may precipitate an attack. Tests with TEA, dibenamine, and benzodioxane produce sharp falls in blood pressure. Perirenal air insufflation may delineate an adrenal tumor mass. The electrocardiographic findings during an attack may show only an increased heart rate Short periods of supraventricular or ventricular tachycardia, or ventricular extrasystoles, have been observed Alterations in T waves are not striking. A left ventricular strain pattern may appear eventually.

ACUTE ADRENOCORTICAL INSUFFICIENCY: WATERHOUSE-FRIDERICHSEN SYNDROME. A small percentage of cases of acute septicemia (meningococcemia, staphylococcemia or gonococcemia) are complicated by extensive hemorrhage of both adrenal glands Massive adrenal hemorrhage may also occur in the newborn infant Malaise, abdominal pain, petechiae, cyanosis, marked hypotension, and shock develop rapidly.

The Pancreas. THE CARDIOVASCULAR COMPLICATIONS OF DIABETES MELLITUS. Diabetes mellitus is a disturbance in the utilization of carbohydrates which is associated with hypofunction of the islet cells This disorder is most important because of its frequency and its serious complications

The duration and degree of diabetes greatly influence the severity of atheromatous degeneration. Thus, coronary artery disease is the most important single cause of death in diabetics. It actually occurs two to five times more frequently in diabetic than in nondiabetic subjects. Marked *arteriosclerosis of the aorta* with uncoiling and widening is fairly common Abdominal aortic aneurysms are likely to develop Fundus changes are eventually discernible in almost every case and consist mainly of microaneurysms. There is a high incidence of arteriosclerosis obliterans in patients with diabetes mellitus. Almost one-third of diabetics of 10 years' (or longer) standing show absent pulsations in one or more extremities. A high rate of hypertension occurs among diabetic patients especially when diabetes is long-standing Congestive failure due to hypertensive and arteriosclerotic heart disease is fairly frequent Earlier diagnosis, new types of insulin (including oral preparations), and the recognition and treatment of extrapancreatic factors in the disease may eventually alter the predominating pathological findings. It is not unreasonable to predict that the premature degenerative changes may become considerably modified in the near future.

Electrocardiographic changes are due to the effects of coronary sclerosis Reversible changes in the electrocardiogram in diabetic acidosis consist of S-T depression, lengthening of the Q-T interval, and inversion of the T waves. The factors which affect the heart are complex and include the disturbed relationship between extracellular and intracellular electrolytes, impaired cardiac nutrition, and the effects of hypoxia and azotemia.

It has long been recognized that, in the late phases of diabetic acidosis, the patient's blood pressure may fall to low levels This change is often irreversible and leads to death within a few hours, it is due to decreased total peripheral resistance, which is below 50 per cent of the normal value The site of this vasodilatation has not been determined The cool, pale skin suggests that cutaneous blood flow is diminished. Electrolyte imbalance, especially of potassium, appears to play an important role.

Renal lesions occurring in diabetes are also important because of their effects on the cardiovascular system Three types of nephropathies are recognizable in diabetes pyelonephritis, arteriolar nephrosclerosis, and intercapillary glomerulosclerosis. Approximately one-third of all diabetic cases with hypertension are associated with intercapillary glomerulosclerosis. This entity is characterized by hyaline deposits between the capillary loops but without associated inflammation or thickened capillary basement membrane

THE EFFECTS OF HYPOGLYCEMIA ON THE HEART (HYPERINSULINISM). When the circulatory glucose is reduced to subnormal levels, the

for the maintenance of a state of good health (see also Chap. 11). These include the proper amount and distribution of organic (proteins, carbohydrates, and fats) and inorganic (minerals) nutrients, as well as the accessory food factors (vitamins).

Endogenous factors concerned with proper nutrition are the adequate digestion and absorption of foodstuffs, hormonal balance, and possible disease of many organs. For example, pancreatic disease may interfere with carbohydrate metabolism, myxedema may allow an excessive accumulation and deposition of fat calories, or sprue may interfere with the metabolism of several nutritive substances.

Exogenous factors include an overabundant or deficient supply of these substances Thus, the spectrum of nutritional disorders which may affect the cardiovascular system ranges from a marked excess to a severe deficiency of any nutrient. In some instances, a single substance may be involved, such as a high level of fat intake However, in most instances, a combination of disturbances occurs. Thus, the influence of starvation may lead to multiple deficiency states. These disturbances will be discussed under two general headings. undernutrition (starvation) and overnutrition (obesity)

Undernutrition. Undernutrition is a problem which constantly affects large segments of the world's population It may assume huge proportions during famines, economic depressions, or wars At other times, it depends upon the uncertainties of climate, nomadic peregrinations, and difficulties in food preservation and transportation Individual factors include the presence of many disease states and the efficiency with which essential materials are utilized Extremes in temperature are also significant since a cold environment increases caloric requirements. Heavy labor demands a greater caloric intake An empty pocket will lead to an empty stomach in any climate. The effects upon the cardiovascular system are few but of enormous consequence. The significance of drastic food restriction over a prolonged interval cannot be overemphasized. The following effects on the heart and blood vessels will be discussed. atrophy of the heart, effects on the blood pressure and cardiac function, nutritional edema, and vitamin and mineral (electrolyte) deficiencies

ATROPHY OF THE HEART. Atrophy of the heart is an integral part of undernutrition and starvation. It may be also associated with neoplasms, chronic infections, and degenerative, metabolic, or endocrine diseases Important factors in the production of emaciation are prolonged illness, bedfastness, fever, surgical procedures, radiation, and gastrointestinal dysfunction. Extreme emaciation is characteristic of anorexia nervosa, Simmonds' cachexia, and Addison's disease.

Pathologic studies recognize two types of atrophy of the heart with about equal incidence *Simple atrophy* is devoid of cellular pigmentation and occurs in younger individuals (average 42 years). The average heart

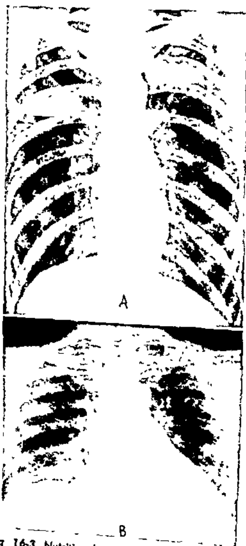


Fig 16-3. Nutritional effects on the heart A. Starvation. B. Obesity.

Right-sided failure is more common than left-sided failure, due to the larger iron content usually found in the right ventricular myocardium. Since these patients exhibit a narrow margin of balance between glycosuria and hypoglycemia, hypoglycemic shock may precipitate failure in a greatly damaged heart.

Primary Xanthomatosis. Primary xanthomatosis is a hereditary disease of the reticular cells due to an intracellular disorder of cholesterol metabolism. Most cases occur in persons under 30 years of age. The serum cholesterol of all relatively young patients with coronary atherosclerosis should be determined as the initial step in uncovering hypercholesterolemia in members of the immediate family. Two types of xanthomatosis are found: that with elevated blood cholesterol level and that with normal level. The former is associated with cardiovascular damage and is considered to be the only familial type of heart disease Although the hereditary nature of this condition has been emphasized by many authors, the mode of transmission is under discussion. Genetic analysis supports the concept that the disturbance of cholesterol metabolism is inherited as an incomplete dominant trait.

The *hypercholesterolemic type* is characterized by cardiovascular involvement, xanthoma of the tendons and tendon sheaths, skin, and bile ducts, with secondary jaundice and biliary cirrhosis, and reticuloendothelial system involvement. The circumscribed, soft, yellow-pink, subcutaneous tumors and the marked elevation of the blood lipids should direct attention to possible cardiovascular involvement, since it has been found that 40 per cent of these patients present coronary artery or peripheral vascular disease. Cardiac symptoms usually develop before the age of 50 *Substernal pain* is a frequent symptom, and electrocardiographic studies reveal progressive changes associated with coronary insufficiency or occlusion. Xanthomatous infiltration may affect the aorta and the cardiac valves causing the production of murmurs Microscopically, large deposits of fatty material are found in the myocardium, in the intima of the coronary and large arteries, and in the valves

Porphyria. Porphyria is a constitutional disturbance of the porphyrin metabolism. The congenital (light-sensitive) form is quite rare but the intermittent acute form is more common. Symptoms usually appear during the second or third decade. The fundamental physiological derangement in acute porphyria is probably due to the occurrence of generalized angiospasm. The vascular changes which occur in acute porphyria have been fairly well established. Hypertension and renal changes, probably due to arteriospasm, occur frequently Nervous manifestations are also common. The red urine which attracts attention to the disease is caused by the presence of uroporphyrin

Ochronosis. Ochronosis is a disturbance of the intermediary metabolism, it is characterized by gray or black pigmentation of all cartilaginous structures, ligaments, and fibrous tissue. Alkaptonuria or melanuria may be found The urine may reveal homogentisic acid, and skin biopsy shows melanin pigment. In the chronic form of the disease, there is a tendency for premature systemic arteriosclerosis to develop.

Gout. The gouty diathesis is a hereditary, constitutional disease associated with a disturbance in purine metabolism, and is frequently characterized by recurrent attacks of acute arthritis due to deposits of sodium urate It is almost entirely limited to men and may occur at any age but is most common during the fourth decade. Hyperuricemia and diminished renal excretion of uric acid are the outstanding laboratory findings Urate deposits may be found in many structures, such as the ears, bursae, and tendons. Their presence has also been reported in the aorta, myocardium, and aortic valves. A foreign-body inflammatory reaction results, which varies in extent and degree with the vascularity of the affected tissues It is well known that the incidence of arteriosclerosis and hypertension is high in gouty subjects Hypertrophy of the left ventricle may result from generalized arteriosclerosis, nephrosclerotic changes, and arterial hypertension Advanced coronary or cerebral vascular disease is frequently the immediate cause of death. Marked arteriosclerotic degeneration of the aorta, terminal pericarditis, and venous thrombosis have also been reported.

NUTRITIONAL DISORDERS OF THE HEART AND BLOOD VESSELS

The body has an optimal daily requirement for the various nutritional factors necessary

lieved to provide insufficient protein for the regeneration of serum proteins, resulting in decrease in the plasma colloid osmotic pressure. Since transudation is a dynamic process, the reduction in serum protein concentration may not be appreciable even with clinical edema. Total serum protein and albumin concentrations of 5 and 2.5 Gm/100 ml respectively, are considered to be the critical levels below which frank edema may be expected to disappear. It is possible that organic changes in the capillary walls provide an additional factor. Nutritional edema must be differentiated from that of congestive heart failure and that of beriberi heart disease.

VITAMIN DEFICIENCIES. Accessory food substances are necessary for the proper metabolism of individual cells and for the catalysis of vital cellular processes. Small amounts obtainable from exogenous *sources are essential*. Specific vitamin deficiencies may occur singly or in combinations during various malnutrition states. Latent or clinically manifest deficiency diseases may affect the normal or diseased cardiovascular apparatus. Unsubstantiated claims and misinformation have been propagated in this particular field. Various vitamin deficiencies as they relate to the heart and vessels will be considered below.

Thiamine Chloride Deficiency (Beriberi Heart Disease). It has become increasingly clear that the manifestations of *beriberi are* subject to great variations. At least three *syndromes* are recognized. *Dry beriberi* is revealed by peripheral neuritis and other nervous system changes while *wet beriberi* presents edema and serous effusions. We are primarily concerned with "beriberi heart *disease*." The disease develops gradually after the patient's subsistence on a grossly deficient *diet for at* least 3 months.

Pathologic changes, e.g., hydropic degeneration *of the* myocardial and conducting fibers, swollen collagen, and interstitial edema with separation of the myocardial bundles, occur *but* are neither specific nor consistently present. *Myocardial fibrosis has* usually been ascribed to diminution of the myocardial blood supply which leads *to scattered* areas of degeneration and replacement fibrosis. Endocardial fibrosis has also been a *frequent* finding. The right-sided chambers of the heart are usually dilated. The heart weight may reach well over 600 Gm. Mural thrombi are frequently found.

Clinically, two types of beriberi heart disease are described. The *acute fulminating form* appears suddenly and results in death when untreated. The more common type is more *chronic* in character and results in congestive heart failure. The following features are necessary to establish a diagnosis of beriberi heart disease: (1) enlarged heart with sinus rhythm; (2) dependent edema; (3) elevated venous pressure; (4) nonspecific electrocardiographic changes, (5) history of 3 or more months of a diet deficient in thiamine; (6) signs of neuritis or pellagra, (7) absence of other causes of heart disease; (8) therapeutic test with clinical recovery and return of heart size and electrocardiogram to normal, or (9) *autopsy* findings consistent with beriberi heart. Cardiovascular manifestations include *dyspnea*, palpitation, tachycardia, and edema. The heart is *often enlarged*, primarily by edema of its wall. However, small hearts are more often seen in the United States. The right or, less commonly, the left ventricle may fail. In occasional *cases, positive* findings are predominantly found in the peripheral circulation and consist of bounding pulse, rapid circulation, overdistended veins in the neck and legs, pistol-shot sounds over the arteries, and sudden circulatory collapse. Thyrotoxic heart disease, nonspecific myocarditis, and neurocirculatory asthenia must be differentiated.

Laboratory studies supply important corroborative evidence. Electrocardiographic changes include bradycardia, *low voltage* of all waves with inversion of T waves, and prolongation of the Q-T interval. The ad*ministra*tion of thiamine chloride results in a *prompt* return to normal and, hence, aids in the *differentiation* from hypothyroidism, which produces a somewhat similar tracing. *Roentgenograms* show a diffuse enlargement of the heart. The right side is usually larger than *the left* and the pulmonary *conus* may be prominent. These changes are also reversible with specific therapy. *Rapid* arm-to-tongue circulation time in the presence of increased venous pressure helps to differentiate *this* from other types of heart failure. Determination of the thiamine concentration of *the blood* or urine, and cal-

weight is 200 Gm. The ratio between heart weight and body weight is 0.48 per cent (normal 0.43 to 0.40 per cent). *Brown atrophy* reveals characteristic bipolar pigment deposits in the muscle cells and occurs in older individuals (average age 62 years). The average heart weight is 230 Gm. The ratio between heart and body weight is normal. In either case the microscopic examination reveals a reduction in size of the muscle fibers Subsequently, evidences of degeneration appear, such as cloudy swelling and loss of striations.

Clinical findings occur as follows:

1. There are reductions in the heart rate, systolic blood pressure, peripheral circulation, and venous pressure.

2. The atrophic heart appears small (Fig 16-3A) or normal in size, with comparatively weak heart tones.

3 A faint precordial or apical *systolic murmur* of functional nature is present in one-fourth of all cases.

4. There is a strikingly low incidence of symptoms and signs of heart failure. Electrocardiographic findings are more or less constant, revealing a progressive diminution of voltage of all complexes and *prolongation of the Q-T interval.*

5. Blood pressure falls in 75 per cent of normotensive cases, and cardiac function is decreased.

Far-reaching observations of large segments of the European population subjected to chronically deficient nutritional states afforded much valuable information. Animal and human experimental studies have also proved enlightening Reports by both Brozek et al and Keys are especially significant

Normal young men were kept on a restricted protein and total caloric intake but without sodium limitation for six months The average body weight fell 24 per cent, the mean systolic blood pressure fell 11 per cent, the mean diastolic pressure fell about 8 per cent, the mean pulse rate decreased to 37, and the average basal metabolic rate decreased to minus 40 per cent Functional studies revealed that the heart decreased in all dimensions and assumed a more upright position in the chest The total volume reduction averaged 16 per cent and the stroke volume reduction averaged 18 per cent. The venous pressure was not more than 50 per cent of the normal level The margin of safety represented by the ratio of metabolism to the oxygen circulating in the blood fell to one-half the normal average. In the first 3 months of rehabilitation on controlled diets, the heart size returned to its original level but other characteristics of cardiac function showed a relatively slower recovery. The heart appeared to be closer to failure during early rehabilitation than during starvation since the stroke volume of the heart was decreased compared with both control and semistarvation values. Vitamin or protein supplements had no significant effect on the recovery rate of cardiovascular function. After 5 months, the work done by the heart was still about 10 per cent below the control, and only one-half of the lost margin of safety was restored

The vast experience of European observers during the recent war also showed that undernourishment causes decreases in blood pressure and pulse rate in both normal and hypertensive subjects. During recovery, the blood pressure not only returns to normal levels, but may rise to frankly hypertensive levels The extensive observations made in Leningrad before the outbreak of the war and during and following the great siege, are characteristic. During the period of reduced food intake, the incidence of hypertension decreased and, in a large number of hypertensive patients, reduction of blood pressure to normal or near normal levels occurred. This was accompanied by a definite decrease in the incidence and intensity of symptoms commonly associated with hypertension; and precordial pain and myocardial infarction were encountered less often than before the war. With an improved food supply, the incidence of hypertension reached epidemic proportions while the incidence of cardiac insufficiency in hypertensive patients increased. In some hypertensive patients, the disease became much more severe in the poststarvation period than it had been in the presiege period.

Although the primary causative factor appears to be the limitation of total calories, cholesterol and total fat restriction were also significant factors. Since salt intake was not especially restricted, this element was of no special significance in any of these studies

NUTRITIONAL EDEMA. When protein deficiency progresses, a disturbance of nitrogen balance develops, as well as reduced serum protein concentration. Hypoproteinemia leads to generalized edema. The deficient diet is be-

rhea, draining fistula, gastric suction, and repeated use of mercurial diuretics), and sprue Studies on familial periodic paralysis and diabetic acidosis have contributed toward the correlation of electrocardiographic changes and hypopotassemia. The electrocardiographic alterations include *prolongation of the Q-T and P-R intervals*, flattening or inversion of the T wave, depression of the S-T segment, decrease in the amplitude of the QRS complex, intraventricular block, or the occasional appearance of prominent U waves

In hypocalcemic states, such as occur in hypoparathyroidism, acute pancreatitis, sprue, and uremia, the electrocardiogram characteristically shows a *prolongation of the Q-T interval*. A borderline calcium deficiency may be further reduced below the critical level by excessive diuresis caused by mercurial diuretics, coffee, or diabetes

The *trace elements* include magnesium, boron, manganese, iron, copper, cobalt, zinc, phosphorus, iodine, and fluorine The role of trace elements is one of participation in the activities of hormones and enzymes, a role probably analogous to that of the vitamins The catalytic-synergistic action of these minerals with vitamins probably makes the difference in speeding up enzymatic processes upon which the body is dependent for all of its functions Deficiencies of minerals and trace elements may affect virtually every organ Unfortunately, knowledge concerning the effects of the trace elements on the cardiovascular system is quite meager at present

Overnutrition. Overnutrition generally implies an excessive caloric intake which results in obesity Hypervitaminosis D and the effects of excess inorganic elements are appropriately considered in this connection

OBESITY Obesity is a metabolic disturbance which is characterized by the ingestion of calories beyond the normal bodily energy requirements resulting in the deposition of excessive adipose tissue There are approximately 30 million overweight persons in the United States alone Obesity produces anatomic and functional impairment of the heart This places a greatly increased burden upon the cardiovascular system by direct invasion of these structures (fatty infiltration) or by increasing their work load Significant degrees of fatty infiltration are found in 6 per cent of autopsied adults. A weight increase of more than 10 lb produces a marked increase over the expected mortality, which is somewhat greater in men than in women. Actuarial statistics indicate that, because of cardiac and other complications, the average age of the obese at the time of death is only 52 1 years This increased death rate is due, principally, to degenerative diseases owing to such factors as increased resting work fraction of the total metabolism, cardiovascular strain, and the frequency of glycosuria. Fatty hearts are present in the majority of patients with diabetes, and diseases of the gall bladder, liver, or pancreas. Both the internist and surgeon are repeatedly impressed by the fact that the obese patient is more prone to complications following medical or surgical conditions For example, thromboembolic episodes are known to have a far greater incidence among the obese

Excessive food intake usually reflects heredity or family conditioning or has a psychogenic basis Lesions involving the hypothalamus may also lead to obesity It may be associated with endocrine disorders, such as hypothyroidism or hyperinsulinism

Dyspnea may occur on a purely mechanical basis and improves promptly with weight reduction However, the occurrence of dyspnea in the obese should not be viewed indifferently since it may be the first evidence of cardiac embarrassment Considerable controversy still exists as to whether obesity is a factor in hypertension The evidence seems to favor the view that an elevation of both systolic and diastolic blood pressures is a common occurrence in obesity Furthermore, overweight may aggravate a preexisting hypertension, and a moderate drop in blood pressure occurs following weight reduction. Clinical findings associated with coronary sclerosis are much more common in obesity than in control series. When death occurs unexpectedly, it is believed that the circulation has proved inadequate following strain of the cardiovascular system caused by infections, surgery, or other stresses Electrocardiographic findings may reveal low amplitude of the QRS complexes and T waves. The similarity of these findings to those seen in hypothyroidism may prove confusing. However, T-wave changes are usually more marked in the latter condition, and there may be a complete inversion of the T waves in all leads

culation of the thiamine content in the diet and the daily requirement of the patients are of dubious accuracy but may suffice to confirm clinical impressions.

Nicotinic Acid Deficiency (Pellagra). Nicotinic acid (niacin) forms a part of coenzymes I and II which are essential for glycolysis and tissue respiration. A deficiency of nicotinic acid and tryptophane in those exposed to the sun leads to the development of cellular alterations in the gastrointestinal tract, skin, and nervous system which contribute to the clinical picture of pellagra. Although almost 7,000 cases were reported in the United States in 1928, only 804 deaths occurred in 1946. This was due to many factors, the most important of which was improved public health education. Cardiovascular involvement is primarily manifested by electrocardiographic changes characterized by lowering or inversion of T waves. The administration of nicotinic acid results in a prompt return to normal. These changes are metabolic in origin, resulting from coenzyme deficiency in the heart muscle.

Vitamin C Deficiency (Scurvy). The lack of vitamin C produces the clinical picture of scurvy. The deficiency may result in hemorrhage into the various layers of the heart and blood vessels as it does into other structures. Enlargement of the heart and tachycardia may occur due to involvement of the connective tissue of the cardiac muscle. Degenerative lesions of the myocardium have been found in advanced cases. A resultant secondary anemia may also exert its effect on the cardiovascular apparatus. Advanced cases with hypertrophy of the right ventricle as well as cases of sudden death in children are on record.

Vitamin D Deficiency. A deficiency of vitamin D produces rickets, with its many characteristic skeletal deformities, as a result of the alterations in calcium-phosphorus metabolism. It produces no direct effects on the cardiovascular apparatus. However, bony deformities of the thoracic cage, such as funnel or pigeon chest and marked kyphoscoliosis, may eventually result in *chronic cor pulmonale*.

MINERAL DEFICIENCIES (ELECTROLYTE IMBALANCE). Deficiencies of various minerals may accompany serious malnutrition, but may also occur in the presence of renal or gastrointestinal diseases and certain hormonal disturbances (adrenocortical disturbances, hyperparathyroidism, and diabetes mellitus). Various electrolyte imbalances may result.

Decreased sodium and chloride intakes rarely affect a normal individual because of the efficient conservation of sodium and chloride by normal kidney function. A deliberately decreased sodium intake is an integral part of the treatment of hypertensive states and congestive heart failure. Its probable relationship to adrenal cortical hormones has been recognized. However, chronic salt restriction, further aggravated by the frequent use of diuretics may result in a serious sodium depletion which requires emergency treatment (*low salt syndrome*). A hypochloremic state may also result in refractory congestive heart failure unless it is corrected. Excessive loss of salt in hot weather may give rise to heat cramps or heat stroke.

Although *potassium* is present abundantly in most foodstuffs, a bodily depletion may result following a number of conditions. Myocardial necrosis and leucocytic infiltration followed by fibrosis, have been produced in rats and hogs by means of a diet markedly deficient in potassium, as well as by the administration of large doses of desoxycorticosterone. Similar changes have been found clinically following the treatment of Addison's disease with DOCA.

Familial periodic paralysis is a rare disorder which demands special attention. It occurs in certain families, and attacks are precipitated by a large carbohydrate meal or violent exercise. For some unknown reason, the attack is brought about by the passage of extracellular potassium into the cells of the body, thus producing a sharp drop in the potassium level of the serum. The episode of paralysis which follows a large meal may be due to the uptake of potassium by the liver as it stores glycogen. The clinical picture of *potassium depletion* consists of muscular weakness, partial respiratory paralysis, water-hammer pulse with irregular rhythm, increased pulse pressure, cardiac dilatation, a systolic murmur, and increased venous pressure. The symptoms disappear after administration of potassium. Other clinical conditions associated with low plasma potassium are diabetic acidosis, postoperative states, the cell-building phase which follows massive tissue destruction, the ion-readjustment phase following recovery from the loss of fluid containing electrolytes (diar-

The earliest changes are *elevated and peaked T waves* As serum potassium level rises, an increased P-R interval is noted, which may be followed by *atrial standstill*. Obliteration of the S-T segment with the T wave originating from the S wave is noted progressively. With still higher potassium levels, widening of the QRS complex occurs and a biphasic ventricular complex may be seen. Death finally occurs as a result of the electrolyte imbalance causing cardiac arrest or ventricular fibrillation.

and an occasional depression of the S-T segment. A deep Q wave followed by an inverted T wave in lead III is occasionally confused with posterior wall infarction. In obesity, the T waves in the unipolar precordial leads may be reduced in amplitude to 50 per cent of normal but do not become inverted. Roentgenograms may fail to reveal enlargement since fat deposited on the cardiac surface is usually not visible on the film. However, a small triangular area occasionally seen at the apex is due to a pad of pericardial fat and fibrous tissue. Sclerosis, widening, tortuosity, and aneurysmal dilatation may be visible in the aorta and the large arterial branches, when obesity is associated with marked arteriosclerosis. In extreme obesity, a considerable deposition of fat within the cardiac walls results in an increase of the transverse diameter of the heart (Fig. 16-3B).

HYPERVITAMINOSIS D. The use of large doses of vitamin D in the treatment of rickets and arthritis has resulted in a number of fatalities. The increased calcium and phosphorus levels of the blood serum result in the precipitation of calcium phosphate at abnormal sites (metastatic calcification) similar to those found with the use of excess parathyroid hormone. The pathological state is not unlike that seen in hypercalcemic states associated with hyperparathyroidism, osteomalacia, osteitis fibrosa cystica, osteoporosis, and renal rickets. Excessive *calcification of the aorta and large arteries*, with a predilection for the subintimal zone, may occasionally be seen. Experimental studies have revealed that regressive changes precede the occurrence of demonstrable calcification. The intima may be intact but frequently presents transverse ridges at the selective sites of calcification which may be covered by small thrombi. Amorphous or plate-like deposits of calcific material may be seen about the elastic fibers. In chronic cases, there is a marked fibroblastic reaction with metaplastic bone formation. The media usually shows no changes.

Secondary *myocardial calcification* (different from the primary forms) may also occur following an excessive intake of vitamin D (as well as in other disorders, e.g., Paget's disease). The valves, endocardium, annulus fibrosus, and pericardium may similarly become impregnated with calcium deposits (Fig. 16-1).

The clinical manifestations of hypervitaminosis D include symptoms due to hypercalcemia (anorexia, lethargy, constipation, and so on), as well as polyuria, polydipsia, albuminuria, hyposthenuria, impaired renal function, hypercalcemia, and hyperphosphatemia. Cardiac manifestations depend upon the nature and degree of the calcification. In rare instances, the deposits may be so diffuse as to interfere with proper contractility. Electrocardiographic changes may reveal T-wave changes and decreased voltage of the QRS complexes, as well as a *shortened Q-T interval*. Roentgenologic findings of cardiac calcification are characteristic. Calcium deposits appear as sharply delineated dense shadows. Under the fluoroscopic screen, they are seen to pulsate with the myocardial contractions. The oblique and posteroanterior views are necessary to definitely determine the exact location of the calcification. Valvular calcification usually reveals a circular motion on fluoroscopy and is sharply localized to the position of the cusps or leaflets. Other structures are more diffusely involved.

MINERAL EXCESSES. Excessive ingestion or administration of various mineral substances seldom occurs as a nutritional disorder. Calcium and phosphorus disturbances have already been discussed under hypervitaminosis D. Variations in water and sodium tend to proceed concomitantly and are controlled to a great extent by the regulatory activity of the kidneys. Excessive osmolar concentration of the body fluids occurs when a sodium-rich fluid (such as *sea water*) is ingested or excessive hypertonic saline is administered. Such cases are not uncommon during wars, when ships or planes are destroyed. When the condition can no longer be balanced by urinary excretion, water is drawn from the intracellular compartment, and this eventually results in circulatory failure. Excess of chloride concentration in the extracellular fluid may be induced by parenteral administration of saline solution when water is not ingested for one reason or another.

Hyperpotassemia may result from severe dehydration or the administration of potassium salts in severe renal insufficiency, among other medical causes. Paralysis of the voluntary and respiratory muscles occurs. The ECG is a good indicator of serum potassium levels because this ion is involved in muscular contraction

The earliest changes are *elevated and peaked T waves* As serum potassium level rises, an increased P-R interval is noted, which may be followed by *atrial standstill* Obliteration of the S-T segment with the T wave originating from the S wave is noted progressively. With still higher potassium levels, widening of the QRS complex occurs and a biphasic ventricular complex may be seen. Death finally occurs as a result of the electrolyte imbalance causing cardiac arrest or ventricular fibrillation.

Hyperergic mechanisms in cardiovascular disease

BRAM ROSE

Advances in immunology and hypersensitivity have led to a reevaluation of many diseases of obscure origin, which are now partially explained on the basis of an *immune mechanism* Some disorders of the cardiovascular system fall into this category and are believed to be due to "hyperergic," or to use the commoner term, *allergic processes*.[1] It is the purpose of this chapter to review some of the mechanisms which relate to this concept.

Theoretically, any substance capable of stimulating antibody production may be termed an *antigen*. While the majority are of proteic nature, not only may carbohydrate or lipid act in this manner, but compounds of smaller size and weight are also capable of participating in this process Many of the latter are capable of combining with one of the plasma proteins to form a complex This complex molecule is then antigenic, but the smaller radical is responsible for the specificity of the antibody so formed, and may combine with it. This is known as the "hapten" theory.

As long as a protein is foreign to the organism, it is theoretically capable of stimulating the production of antibodies The well-known immune responses which occur subsequent to invasion of the body by bacteria or other foreign organisms have been regarded as a *protective mechanism*, since antibodies to bacteria may have many attributes such as the neutralization of a toxin, or the enhancement of phagocytosis, to mention but two Their specificity permits diagnostic procedures carried out either in the test tube or in the skin These procedures depend on the fact that the antibody has an affinity for the antigen and forms a complex which, for example, can be seen as a precipitate in vitro, or the induction of a skin reaction when the antigen is injected in the skin. Immediate skin reactions consist of a flare and wheal and are due to the release of histamine The antibodies involved are humoral and circulate in the plasma Delayed responses, which take some 48 hr to appear and consist of a local erythema at the site, are due to a bacterial antibody of which that resulting from *tuberculin* is the prototype As demonstrated by Chase, this form of antibody is cellular rather than humoral. Skin reactions to tuberculin are in effect a local allergic manifestation, and will occur only if the antibody specific for the injected antigen is present. It was this altered reaction to tuberculin which prompted von Pirquet to call this phenomenon "allergy" Nevertheless, individuals giving such responses are not necessarily allergic in the ordinary sense of the term.

With the developments consequent on the description of *serum sickness* in man and *anaphylaxis* in animals, the whole concept of allergy began to take form, since it was soon realized that the common denominator of allergic disease was the combination of an anti-

[1] The interconnected aspects of "hyperergic" and "allergic" disorders, and the "diseases of the collagen system" are discussed in this and the next chapter. *Editor*

gen with its specific antibody This is, however, the basis of immunity as well. *It is difficult, therefore, to define the borderline between these two states.* There are certain general criteria which differentiate the allergic response from the immune reaction. Some of these are discussed below.

SELECTIVITY, OR HEREDITARY FACTORS

Allergic manifestations of the common variety, such as the hay-fever–asthma–urticaria variety, occur in an estimated 7 per cent of the population. The tendency is hereditary in the majority of cases. In a similar fashion, only 15 per cent of those infected with group A hemolytic streptococci develop rheumatic fever or glomerulonephritis There are many forms of hypersensitivity, however, which do not seem to follow this pattern, they occur in patients devoid of any previous allergic tendency or family history of allergy. The nature of the inherited or acquired metabolic change which allows hypersensitivity to develop is quite obscure. Clearly, other factors are often involved, particularly the nature of the antigen or the type of invading organism. For example, individuals residing close to cottonseed growing or processing develop a high incidence of allergy to this substance Similarly, Lancefield A streptococci, type III, may give rise to a much higher incidence of glomerulonephritis than other types.

ALLERGENS (ANTIGENS)

Individuals with an allergic background may develop sensitivity to substances which in general are harmless to the rest of the population These include foods, pollens of many varieties, and drugs It is clear that other antigens, such as bacteria of one sort or another, fall into this category as well. However, since not only may evidence of the infection be present but allergic manifestations, such as asthma, acute rhinitis, or urticaria as well, it is possible that some additional form of antibody response takes place in allergic patients This concept is supported by the well-known fact that almost all antigens are impure in the sense that they are complex in nature and, therefore, may give rise to multiple antibodies. Since the allergic individual is characterized by the fact that he is prone to develop antibodies easily, the response may be a different one However, the tendency to develop conventional antibodies in quantities greater than normal was not found to exist in patients with rheumatic fever. Another manifestation is the eosinophilia which accompanies most, although by no means all, allergic responses. In this connection, it is believed by Speirs that the eosinophil may give rise to antibodies, but the exact significance of this cell is not yet known.

NATURE OF THE RESPONSE

It is characteristic of the allergic or hyperergic response that the pattern of the lesion bears little or no relation to the properties of the inciting antigen. For example, polyarteritis may be precipitated by a variety of different allergens including drugs, bacterial infections, or parasitic infestations The same is true for various allergic skin lesions as well as the commoner forms of allergy such as asthma.

As will be pointed out below, it is possible to vary the response in the experimental animal by means of a selective antigen Thus, one can induce antiserums with an affinity for the various cellular elements of the blood, the kidney, and thyroid or other special tissues. Of particular importance in this whole concept is the fact that, in early experiments, it always seemed necessary to use a second species. Thus, in order to induce a form of glomerulonephritis in the dog, it was necessary to inject extracts of dog kidney into a second species, to which the tissue was foreign. The recipient of the foreign tissue would then produce an anti-dog-kidney serum which, when administered to a dog would combine selectively with kidney tissue, thereby inducing lesions. It is now possible to induce such lesions without resorting to a second species, using homologous tissue. This represents a marked advance in the study of "immune" mechanisms in terms of human allergic disease.

ANTIBODY FORMATION

It is now generally accepted that most, if not all, antibodies consist of gamma globulin with an immune specificity. The source of antibody is a question of some debate. In general, it is believed that antigen finds its way to some part of the reticuloendothelial system, there to be taken up and transferred to the

lymphocyte. In this cell, it exists in a precursor state. Whether the lymphocyte actually transfers it to the plasma cell, or indeed, as believed by Dixon, the lymphocyte is the actual precursor of the plasma cell itself, is not firmly established. It is, however, agreed generally that the ultimate source of gamma globulin or antibody, as the case may be, is the plasma cell. It seems probable that there are other sources of antibody since patients with *agammaglobulinemia,* who are also devoid of plasma cells, appear to develop skin reactions of an allergic nature as well as resistance to some viral infections.

EFFECTS OF COMBINATION AND NATURE OF LESIONS PRODUCED

The combination of antigen with antibody may give rise to a variety of effects depending on the nature of the complex, the site of combination, and the type of metabolite released. In the case of the common forms of allergy, which are due to foods, inhalants, or in some instances drugs, skin-sensitizing antibody is involved, and it is believed that *histamine,* as well as other metabolic substances, may be released at the site of combination. *The cardiovascular system participates in the reaction in that capillary dilatation and increased permeability occur in association with smooth muscle spasm* In the majority of cases, these are minor and reversible However, acute anaphylactic reactions leading to rapid *vasomotor collapse* may occur. In those cases where ECG tracings have been obtained, minor, nonspecific changes of a reversible nature have been found On a similar basis, *extrasystoles,* other forms of *arrythmias,* and *tachycardia* have been reported from time to time as being caused by certain foods

In acute animal experimentation, with the production of anaphylaxis by means of sensitization with a foreign protein, production of precipitating antibody, and eventual anaphylactic shock following the injection of the shock dose of antigen, it is now believed that the mast cell is the target organ This cell contains *histamine, heparin,* and *serotonin* (5-hydroxytryptamine). What role serotonin plays in the anaphylactic reaction is not yet clear It is released in considerable quantities during anaphylaxis in the rabbit and rat A remote but possible role for serotonin is the *induction of* valvular lesions. Thus, right-sided valvular defects, which occur in patients with the clinical syndrome of *carcinoid,* are thought to depend on the presence of large amounts of serotonin in the blood. Whether this bears any relation to the valvular lesions which occur in rheumatic heart disease or those of disseminated lupus erythematosus is unknown. Depending on the animal species used, the predominant metabolite may be histamine, as in the guinea pig, or serotonin, as in the rat. The rabbit appears to release both substances. The so-called "shock organ" also varies from one species to another. In this respect, man seems to differ somewhat since the shock organ varies from one individual to another. For example, hypersensitivity based on pollen or drugs may give rise to lesions involving the sinuses, lungs, skin, joints, or small blood vessels The reasons for this are not clear unless it be due to the actual location of the antibody in a particular tissue.

EXPERIMENTAL ARTERITIS AND CARDITIS

The induction of lesions in the arteries and heart by means of a massive injection of horse serum was demonstrated in the classical observations of Rich. Confirmation and extension of these studies by many others soon followed, and the lesions so produced were found to be quite similar (if not identical) to those found in *polyarteritis* in man. The lesions consisted of classical necrotizing arteritis, with fibrinoid degeneration involving all coats of the arteries and arterioles, round cell and eosinophilic infiltration, granulomatous changes, and nodules similar to Aschoff bodies in the myocardium These lesions were thus firmly placed in the category of hyperergic reactions, and many examples due to serum disease or hypersensitivity to drugs were thought to be due to a similar mechanism in man. It is of some interest that a selectivity for the heart vessels could be demonstrated by Hawn and Janeway, who found that injections of bovine serum albumin into rabbits induced cardiac lesions predominantly. Injections of bovine serum gamma globulin, on the other hand, resulted in kidney lesions. Whether large doses of foreign protein are used, as shown by Rich and Gregory,

or bacterial cytoplasm or toxoid, recently used by Cohen, arteritis of one description or another can be produced

It had been postulated that glomerulonephritis and rheumatic carditis were due to the results of antigen-antibody combination (Cavelti). Using a collodion particle method and emulsions of human heart muscle or kidney as antigen, the Cavelts claim to show antigen-antibody combination in vitro, using serum from cases of rheumatic fever or glomerulonephritis The test was negative when normal serums were used This work, however, could not be confirmed by others at the time. On the other hand, by using a different technique, Stefanini was able to demonstrate the presence of antibody for human blood vessels in the serums of patients with periarteritis He used fresh aorta and large arteries obtained from stillborn children as the antigen When an extract of these was added to the serum of patients with polyarteritis, a precipitate formed On the basis of these observations, it was postulated that, in patients with vasculitis, an initial change in some part of the vascular tree arises, with the result that some component is regarded as foreign This is then dealt with by the body as is any other foreign protein, with the subsequent production of antibody specific for blood vessels The antibody then combines with the blood vessels, producing the typical lesions

Based on the fact that antibody is in almost all cases an immunologically altered gamma globulin, an attempt was made to demonstrate the existence of gamma globulin itself in the lesions of the various types of so-called *collagen disease* An antiserum to human gamma globulin was made by injecting the latter into rabbits This rabbit antihuman gamma globulin was then labeled with fluorescein by the Coons technique so that it could be visualized in ultraviolet light When this labeled serum was allowed to come into contact with sections of tissue from cases of polyarteritis, disseminated lupus, or of the heart from cases of rheumatic fever, gamma globulin could be shown to exist in the lesions by the marked fluorescence indicating that the tagged antihuman gamma globulin had combined with the human gamma globulin in the tissue Normal tissues did not show this reaction

All these findings then, while they support the theory of hyperergic activity, leave several unanswered questions. The presence of gamma globulin in the lesions of fibrinoid degeneration or arteritis implies that the gamma globulin either contains, or is in essence, the antibody specific for the tissue involved. This has as yet not been demonstrated directly. It is remotely possible, for example, that the gamma globulin is precipitated in these lesions for reasons other than an immune process.

From the foregoing, it seems clear that there must be at least two distinct types of antibody which, by forming antigen-antibody complexes, may involve the cardiovascular system. *The first is dependent on the effects of such a complex derived from some outside source, such as common allergens (foods, pollens, drugs, or serum) combining with the specific antibody involved, or that which occurs following the injection of a foreign serum.* Under these circumstances, elements of the vascular system may be termed the shock organ In the case of foreign serum injection in the experimental animal, Germuth has shown that the lesions form rapidly during the period of antigen excess and before the production of antibody. As the latter forms, some of the lesions begin to regress However, the exact mode by which arteritis, myocarditis, as well as Aschoff-nodule-like lesions are formed is not clear It has been shown that smooth muscle and capillary endothelium play a prominent role. There may thus occur vasoconstriction of arterioles, slowing of the circulation, and a tendency for leucocytes to adhere to the endothelium with migration through endothelial walls. Local edema may also occur According to Germuth, some lesions are due to the actual intravascular precipitation of antibody with antigen. However, by whatever means the various structures of the heart and vessels are affected, the situation is in a sense nonspecific, since lesions may arise as the result of many foreign antigens. The *Arthus phenomenon* is in a similar category. Reference to the *Shwartzman phenomenon* is made only to state that while this reaction is extremely interesting, there is little to support the contention that it depends on the formation of antibody, or on other immune mechanisms.

The second means by which lesions of the

cardiovascular system may arise on an immune basis is predicated on the formation of "autoantibodies." *This postulates that the actual tissue involved, some component of heart muscle or its connective tissue, for example, behaves as an antigen.* Thus, antibody formed as a result selectively seeks out the original tissue responsible. That such a possibility might exist was for years an unacceptable concept and was referred to as "horror autotoxicus" by Ehrlich. However, as newer evidence has accumulated, this type of response is providing an explanation for the lesions of a growing number of disease entities. Thus, Dameshek has recently reviewed the immune mechanisms relating to disseminated lupus erythematosus, and a similar discussion was presented by the author. Using the tissue of an animal, and some medium such as Freunds adjuvant, which contains mineral oil and killed tubercle bacilli, it is possible to induce lesions in the same species (or indeed, in some cases, in the animal from which the tissue was originally removed). Depending on the type of tissue used, one can induce lesions of the central nervous system of a demyelinating nature, thyroiditis, aspermatogenesis, ophthalmitis, or glomerulitis.

In man, one of the enigmas which exists is how such autoantibodies may actually arise. There are at least four possibilities:

1. Taking *rheumatic fever* as an example of an "allergic" or "hyperergic" disease, it is established that the cardiac manifestations appear in 2 to 6 weeks after the initial streptococcal infection. This is regarded by some as the period of sensitization. The streptococcus gives rise to the formation of antibody which, in the normal individual, combines with the organism (or some part of it) and ultimately rids the body of the invading organisms This combination of antigen (bacterium) with its specific antibody might induce lesions in the same manner that antibody to foreign serum might do as it combines with the antigen, in the manner described above.

2. Another possibility is that the organism invades the heart muscle or blood vessels, forming a small nidus of infection which might be dealt with as would any other local infection, ultimately leaving a tiny scar However, the tissue involved might, in a suitable patient, be regarded as foreign, since it is now altered by the infective process. If there was sufficient similarity between the altered tissue and normal heart muscle, the antibody so formed might be directed against both with the consequent production of lesions. Such a possibility does not seem likely.

3. A third means by which autoantibody might arise depends on the structural similarity between the mucopolysaccharides of tissues and those found in bacterial antigens With antibodies formed to combat the latter following infection, they would have an affinity for not only the streptococcus but certain elements of heart tissue or blood vessel as well. Consequently, lesions might again be the result of a complex formed between antibody and cardiac tissue. Such a possibility is quite logical in the light of work concerning the *mucopolysaccharides*, and could also explain the selectivity of patients For example, it is probable that there is a difference in the mucopolysaccharides of certain tissues, such as heart or blood vessels, of those individuals who are prone to attacks of rheumatic fever, as compared to those who do not develop this disease.

4. In terms of certain work, particularly that of Roitt, who has shown clearly that antibody to thyroglobulin is present in the serum of patients with *Hashimoto's disease (thyroiditis)*, it is conceivable that a similar mechanism may prevail in the production of lesions in other tissues of the body. Apparently, certain tissue complexes, of which thyroglobin is an example, are "foreign" to the body of the individual or animal in which they reside This implies that, under normal circumstances, thyroglobulin is retained within the thyroid capsule during the entire lifetime of the individual. As such, it does not circulate Should it for some reason escape into the circulation, it is treated as a foreign protein, and stimulates antibody production. This antibody has a specificity for thyroglobulin and returns to the thyroid, forming a complex with thyroglobulin and further damaging the tissue. It is not known how the original lesion begins, but clearly this disease must depend upon some alteration in the metabolism of the individual concerned, otherwise one might expect the condition to appear much more frequently, for example after operative procedures to this gland. However, this is a characteristic of allergic disease in general. Such a mechanism

as has been demonstrated in the case of the thyroid could quite conceivably explain lesions in other parenchymal tissues, such as heart or blood vessels

One of the tenets of all allergic mechanisms is the demonstration of antibody. In the case of thyroiditis, the addition of thyroglobulin to the serum of a patient with this disease results in a precipitin reaction due to the antigen-antibody complex so formed It has not been possible to demonstrate the presence of antibody to any of the elements of the heart, such as pericardium, myocardium, or blood vasculature with the exception of the work of Stefanini, and this has not yet been confirmed

In summarizing the data in a general way, therefore, it would seem that a particular type of individual, with some metabolic deviation, is first necessary Such an individual is prone to develop antibodies to a whole host of factors which do not arise in the nonallergic subject These include not only foods, pollens, and drugs but also bacteria In terms of the latter, it is entirely possible that, not only are the conventional types of antibodies produced but possibly others which would not arise following infection in a nonallergic subject. It also seems possible that the allergic individual may possess mucopolysaccharides which more closely resemble those of the bacterial antigens in general, than do those of the so-called "nonallergic" subjects The final possibility of autoantibodies has already been speculated on

CLINICAL ENTITIES

Although these will be dealt with more fully in other sections of this book, they are now briefly reviewed in relation to the mechanisms of allergy which are involved

Tachycardia and Arrythmias Cases of paroxysmal tachycardia, extrasystoles, or atrial fibrillation due to allergy to foods have been reported by Kern and Harkavy, as well as others In all of the cases reported, other forms of common allergy were associated, and there were no other diseases, such as rheumatic fever or myocarditis to account for the cardiac symptoms Avoidance of foods by trial and error rather than by skin testing resulted in a disappearance of symptoms These cases are not common in the literature but undoubtedly exist.

Coronary Heart Disease. Reports of attacks of precordial pain due to food hypersensitivity are rare, and it is unlikely (in view of the paucity of such cases) that such a mechanism exists There have been cases in which the administration of a drug (such as aspirin) was associated with severe precordial pain and urticaria In one of these cases, ECG abnormalities, consisting of prolongation of the P-R interval and notching of S_2 and S_3 waves with inversion of T_3 wave, could be induced by the administration of 5 grains of aspirin. These changes disappeared with the cessation of the attack Again, the incidence of such reports in the literature is exceedingly small and, as a result, such cases must either be rare or missed clinically.

Rheumatic Fever and Rheumatic Myocarditis. This is by far the most common form of bacterial allergy giving rise to hyperergic lesions of the cardiovascular system (see Part 7) The disease is characterized by pancarditis, chorea, subcutaneous nodules, erythema marginatum, and polyarteritis. Although it is rare in infancy and old age, cases have been described The organism involved is the *streptococcus* Until recently, it was impossible to isolate organisms from the circulation or serous effusions during the active stages of the disease, but this has been accomplished by means of refined techniques Nevertheless, the incidence of the condition in relation to streptococcal infection, an incubation period varying from 4 to 6 weeks, evidence of previous infection such as the antistreptolysin titer, and antibody capable of agglutinating hemolytic streptococci in high titer, all support the theory that this is an allergic disease

Bacterial Sensitivity, Myocarditis, Pericarditis, and Arteritis. There exists a group of patients, characterized by an allergic background or hereditary trait, in whom mild symptoms such as a sinusitis with vasomotor rhinitis are the first to appear. This soon progresses to asthma, related to the infection, which in turn becomes worse, and is complicated by weight loss and a feeling of malaise As time progresses, pulmonary infiltrations of an evanescent character may be observed by serial x-ray examinations, these are characteristic of so-called *Loeffler's syndrome* or transient pulmonary eosinophilia At the same time, with or without renal involvement, there are myocardial changes with cardiac enlargement, and ECG changes. Some of these patients pro-

gress to a full-blown picture of *periarteritis nodosa*, with fluctuating eosinophilia, fever, muscle pain, and marked debility. Lesions at autopsy consist of a widespread vasculitis including the coronary vessels. Clinically, several forms are recognized, according to Zeek and to Banks.

Various Lesions. It has been postulated that the endocarditis, pericarditis, and arteritis of *disseminated lupus erythematosus*, the vascular lesions of *Wegener's granulomatosis*, as well as such diverse entities as *subendothelial fibroclastosis* and *Fiedler's myocarditis*, could be due to autoantibody formation. These entities, as well as the various types of myocarditis secondary to viral infection, might be due to such mechanisms but there is as yet no direct proof or evidence to support this contention. Finally, many descriptions of so-called "allergic vasculitis," with lesions of blood vessels due to sensitivity to diverse agents, have been reported by McCombs et al. and by Harkavy. In some patients, withdrawal of the offending agent or administration of steroids resulted in a disappearance of the lesions. The fact that the majority of these hypersensitivity diseases are associated with an elevation of the gamma globulin fraction of the plasma proteins is taken as indirect evidence of abnormal antibody production.

3

Collagen diseases

Cardiovascular Manifestations of Collagen Diseases

MATTHEW TAUBENHAUS AND BERNARD EISENSTEIN

The Heart in Lupus Erythematosus; the Heart in Libman-Sacks Disease

EUGENE LIPPSCHUTZ

CARDIOVASCULAR MANIFESTATIONS OF COLLAGEN DISEASES

The involvement of the cardiovascular system by the pathological processes commonly described as *collagen diseases* is extensive and constitutes an important feature in the diagnosis and differentiation of these entities Despite this, the affections of the heart and vessels may not be apparent to the clinician for a long time, and manifestations of disorders of other organs or organ systems may be in the foreground The validity of the general term collagen diseases has been discussed (Taubenhaus et al). It has been pointed out that reference to the word "collagen" in regard to pathological processes meant a step forward in recognizing a common denominator of these diseases As the physiology of connective tissues was studied more extensively (Meyer, Dorfman; Randall), and the complex interdependence of its various structures was recognized, it was generally felt that the term "collagen diseases" *is not* appropriate because the cells and other fibers, as well as the ground substance, participate in the pathological reactions Moreover, in some syndromes, the striated muscle is primarily and predominantly involved Klemperer (1957) has clarified some points concerning the general terminology.

Cardiovascular manifestations of systemic lupus erythematosus, necrotizing angiitis, progressive systemic sclerosis (scleroderma), dermatomyositis, and serum sickness will be briefly described below The role of certain steroids, which have played an important part in the study of these diseases will also be discussed Rheumatic fever and rheumatoid arthritis, which in many ways fall into the same category, will be omitted. However, it is noteworthy that types of carditis and aortitis have been described in rheumatoid arthritis which differ histologically from the ones found in rheumatic fever (Sinclair and Cruickshank).

It may be stated here that great similarities exist in many of these disorders Fibrinoid degeneration, occasional platelet thrombi, involvement of the small vascular bed, nonspecific inflammatory reactions, and other lesions occur in most of these diseases and it may be difficult for the pathologist to separate clearly the various entities The opinion has been expressed by Beigelman et al that these diseases vary only in the degree of the associated tissue reactions. However, clinically, most of these conditions stand out as more or less definite diseases.

An entirely different group of connective tissue diseases with involvement of the cardiovascular system must be separated from the conditions under present discussion: they are heritable and not inflammatory, and, in particular, no fibrinoid necrosis occurs. These entities (Marfan syndrome, Ehler-Danlos syndrome, etc.) have been reviewed by McKusick (1956).

Considering the origin of collagen diseases in general, the question arises as to whether they can be classified as manifestations of

allergic reactions. In the past, fibrinoid degeneration was thought to be the morphological substrate of an antigen-antibody reaction More recently, it has been pointed out that *fibrinoid degeneration* is not exclusively limited to allergic reactions or diseases. There is even a question as to whether the fibrinoid degeneration is identical in the various diseases. Certain variations of the staining characteristics seemed to point to a variety of materials which constitute the substrate for this histological picture. Plasma fibrinogen forms an important part of fibrinoid.

The histology of allergic reactions has been extensively studied, and indeed certain analogies have been found with the pathology of collagen diseases. The changes can be ascribed to an antibody-antigen reaction and usually begin within the vascular bed. Initially, there is an alteration of the blood flow through capillaries with adherence of leucocytes and platelets to the vessel wall, and increased capillary permeability Antibody molecules (labeled with fluorescent tags) can be seen accumulating in the perivascular spaces around the small arteries Necrosis and secondary inflammation follow, and constitute the experimental *allergic angiitis.*

Electron-microscope studies of the affected collagen tissues, following an Arthus phenomenon, reveal changes in the fibers. Some diseases, such as serum sickness and certain types of necrotizing angiitis, have most likely an allergic pathogenesis and represent the clinical counterpart of the experimentally induced allergic processes In *systemic lupus erythematosus,* certain features point to active immune-biological reactions Serum obtained from patients with this disease is capable of inducing specific morphological changes in the nuclei of polymorphonuclear leucocytes in vitro. A gamma globulin which has a specific affinity for isolated cell nuclei and nuclear nucleoprotein is the responsible serum factor Fluorescent antibody technique has demonstrated the localization of the globulin on cell nuclei during this reaction (Holman and Kunkel; Friou) Of interest has been the production of a syndrome similar to systemic lupus erythematosus, with the appearance of L.E. cells, caused by prolonged administration of hydralazine In rheumatoid arthritis, dermatomyositis, or progressive systemic sclerosis, there is no evidence of allergic etiology. One of the outstanding features, which particularly distinguish the latter collagen diseases from the true, usually self-limited, allergic reactions, is their perpetuation and self-maintenance over a period of years. The reason for this phenomenon is completely obscure.

SYSTEMIC LUPUS ERYTHEMATOSUS (S.L.E.)

The knowledge of this disease has been considerably enriched by the attempt to recognize its pathophysiology (Klemperer, 1955) and the discovery of the L.E. phenomenon (Hargraves, Haserick). The diagnosis can now be made early and the course of the disease studied over a period of years The signs and symptoms may be protean, and years may elapse before cardiovascular involvement becomes clinically manifest. Vascular involvement may exist even in early stages and can be recognized by biopsies of the skin, liver (Dubois, 1952), the kidneys (Muehrke et al), and, rarely, the skeletal muscle The pathological studies of the cardiovascular manifestations show certain characteristics which facilitate the diagnosis and explain some of the functional impairment In the medium-sized and smaller vessels there is a subendothelial fibrinoid necrosis of the vascular wall which may involve the entire thickness of the vessel Actual occlusion of the lumen by thrombosis is rare, but swelling of the vessel wall may cause narrowing of the lumen and impaired blood flow. Fibroblastic proliferation occurs but it is quite characteristic that the inflammatory reaction in and around the necrotic portions is minimal. Hemorrhagic diathesis is common, due to the vascular lesions, in addition to the coagulation defects and the thrombocytopenia commonly associated with this disease. In the spleen the lesions are commonly found in the penicillary arteries and are characterized by periarterial fibrosis. Serial renal biopsies have demonstrated that the characteristic *wire loop lesions,* described in the glomerular tufts, probably represent only one stage in the development of the complex lupus nephritis (Muehrke et al).

Involvement of the *heart* itself is usual. Pericardial effusions, fibrinoid degeneration of the pericardium, and epicardial hemorrhages are common. The myocardial lesions are charac-

terized by the typical involvement of the smaller branches of the coronary arteries with focal necrosis of the heart muscle. Diffuse exudative changes compatible with a myocarditis or local fibrinoid degeneration of the interstitial tissue can also be observed. The endocardial lesions consist of swellings of the valves, due to fibrinoid degeneration, with formation of *verrucae* These occur on both sides of the cusps and, in addition, are found on the mural endocardium and in the valve pockets Hematoxylin bodies are characteristically found in the valves, but are also seen in other organs.

The clinical manifestations of S L.E. caused by cardiovascular involvement are protean *Raynaud's phenomenon* occurs quite frequently. Central nervous system involvement due to lupus arteritis has been observed repeatedly. Convulsions or hemiplegia may initiate a more generalized symptomatology in some cases. Peripheral neuritis has been observed and may make the differentiation from periarteritis nodosa difficult. Retinal hemorrhages, exudates, perivasculitis (cytoid bodies), embolic petechiae, and occasional arterial occlusion may be found on fundoscopy (Hollenhorst and Henderson) Gastrointestinal hemorrhages and pancreatitis due to lupus *angiitis* have been observed Occasional lupus angiitis can be found in the liver, but the hepatomegaly encountered in this disease is mainly due to parenchymal changes Urinary findings, varying from microscopic hematuria to heavy albuminuria accompanied by hypertension or the nephrotic syndrome may be encountered, depending on the stage and the degree of the renal vascular involvement *Hypertension* due to lupus nephritis is usually seen when renal involvement is sufficient to lead to azotemia Roentgenographic changes in the lung suggesting pneumonitis may be specific and related to the vascular disease (Baggenstoss). Lesions of the *coronary arteries* may give rise to an anginal syndrome or even myocardial infarction *Pericarditis,* with all its signs and symptoms is one of the most common occurrences and can be observed in nearly 50 per cent of the cases *Pericardial effusion* may be prominent and occasionally require repeated paracentesis Endocarditis, widely known since its description by Libman and Sacks (Gross) is commonly encountered in the necropsy material Clinically, it is usually silent. Systolic murmurs are frequently heard but difficult to evaluate because of fever, tachycardia, and anemia which are present in most cases Diastolic murmurs in the mitral and aortic region can be heard and are probably due to verrucous endocarditis. Bacterial endocarditis may be engrafted on these verrucae. Cardiac enlargement is frequent and related to the myocardial involvement. Congestive failure is common The electrocardiogram reflects the underlying pathologic process occurring in the pericardium and myocardium Accordingly, the most typical changes are those indicating diffuse pericarditis. Transient T-wave flattening and inversion in various leads associated with intermittent prolongation of the P-R interval would reflect multiple focal areas of myocarditis In some cases, where confluent necrosis is present, classical infarct patterns may be observed (Taubenhaus et al.).

NECROTIZING ANGIITIS

Necrotizing angiitis is characterized by a systemic involvement of the vascular tree and most of the manifestations of this condition are attributable to the vasculitis In general, the characteristic lesion consists of disseminated areas of focal or segmental *fibrinoid necrosis involving all* three layers of the arterial and venous walls It is accompanied by a pronounced inflammatory reaction, which, depending on the stage and type of the disease, may exhibit polymorphonuclear leucocytes, round cells, eosinophils and giant cells in varying amounts The inflammatory exudate may extend beyond the adventitia and surround the vessels like a cuff. Thrombosis of vessels and *fibrosis* in later stages is characteristic. Due to the loss of continuity of the structure of the vascular wall, *microaneurysms* form, and rupture of the vessels with perivascular hemorrhage may occur

A considerable amount of experimental work has been done to elucidate the causes of the vascular lesions Some investigators interpreted them as the pathological substrate of *antibody-antigen reactions,* in which circulating globulins deposited in and around the vascular wall play a major part (Ehrlich). In certain types of angiitis (see below) the antigenic origin may very well be applied, although in others no such evidence exists Hypertension may be

a factor under special circumstances. In human beings, hormonal factors (Selye 1951), in particular the mineralocorticoids, have not been proved to be of etiological significance.

An attempt has been made to outline various entities within the syndrome on the basis of certain etiological, pathological, and clinical aspects. The following four groups of primary angiitis have been characterized: (1) hypersensitivity angiitis; (2) allergic granulomatous angiitis; (3) periarteritis nodosa; and (4) temporal arteritis. These subdivisions, although helpful, are not entirely satisfactory, as frequent overlapping occurs, and cases which may not fall into any of these categories are frequently observed.

Hypersensitivity angiitis (Zeek; see Chap. 2) may occur in response to parenteral administration of foreign proteins and certain drugs (sulfonamides, iodine, Dilantin, and propylthiouracil). It is probably the clinical counterpart of vascular lesion produced experimentally (Rich and Gregory) Small arteries, venules and precapillaries are involved. All the lesions appear to be of the same age. The most common sites of involvement are the kidneys, cardiac muscle, lungs, and spleen. Necrotizing glomerulitis is quite common. The diagnosis is often difficult because of the underlying disease, for which the drugs were administered The course is rapid and frequently fatal Fever is always present and the skin is commonly affected by petechiae and urticarial eruptions. Cardiac manifestations, such as congestive failure, occur and may be due to multiple miliary infarcted areas in the myocardium. Nephritis with hematuria and azotemia is prominent The pulmonary involvement can be observed roentgenologically and may appear as areas of pneumonitis Splenomegaly may be seen. The manifestations described above are encountered in the most severe cases, little is known about milder forms, which are transient and heal without permanent damage to the organ function. Such reversible states, in which the diagnosis was established by biopsy, have been described by McCombs et al. Transitions from such mild forms to the more severe ones are probably common

Allergic granulomatous angiitis (Churg and Strauss) involves smaller arteries in various organs causing vascular occlusion and infarction. It is associated with asthma, fever, and eosinophilia. This disease is characterized by abundant eosinophilic reaction in and around the necrotic vessels and also by extravascular granulomas exhibiting fibrinoid necrosis, eosinophilia, and giant cells. The distribution is similar to that of hypersensitivity angiitis except that the lesions are at different stages of development indicating their varying age Involvement of the mesenteric vessels with formation of aneurysms is common Clinically, multiple organ systems are involved. Cerebral and peripheral nerve manifestations and renal involvement are prominent. Death occurs, usually due to uremia, cardiac failure, or cerebral hemorrhage. A separate entity has been outlined by Wegener (Fahey et al) which is similar to the allergic granulomatous type, except that severe inflammatory and necrotizing disease of the paranasal sinuses is coexistent. Possibly also cases associated with eosinophilic pneumonia and enormous leucocytosis have a similar pathogenesis. In the latter, the renal vascular involvement may not be prominent (Engfeld and Zetterstrom).

Periarteritis nodosa is the most common type of necrotizing angiitis Its cause is unknown The small as well as the medium-sized arteries or veins may be involved. Foci are found in the renal, coronary, mesenteric, and muscular arteries; the splenic and the pulmonary vessels are usually spared. *Microaneurysm* formation is common. Histological evidence of myocardial necrosis is common, although the coronary arteries may be involved without clinical evidence of myocardial infarction (Sinclair and Nitsch). The papillary muscle may rupture due to infarction. Renal infarcts are quite common and necrosis in any organ may occur due to ischemia. The disseminated involvement in various organs gives rise to the protean manifestations of periarteritis nodosa Ulcerations of the skin, focal necrosis of the skeletal muscles with pain and tenderness, are not unusual Peripheral neuritis and cerebral vascular accidents are common. Gastrointestinal bleeding and hepatic involvement has been observed (Mowrey and Lundberg). Cardiac hypertrophy and dilatation with congestive failure and retinopathy may be partially secondary to renal involvement and hypertension. Congestive failure is the most common cause of death, followed in frequency by

uremia and "stroke" Serial electrocardiographic tracings may, depending on the cardiac involvement, show more or less typical evolution of pericarditis, myocarditis, or myocardial necrosis More commonly, nonspecific ST-T and P-R changes are seen When hypertension and renal disease are the predominant manifestations, evidence of left heart strain or electrolyte disturbance may appear

Temporal arteritis, as described by Horton, is usually confined to the cranial arteries, although involvement of other vessels such as the coronaries, the aorta or the larger muscular arteries may be observed on occasion (Cooke et al, Morrison and Abitbol). Its pathogenesis is also unknown and again little evidence exists that allergic or hypersensitivity factors play a role Fibrinoid necrosis of the vascular wall with inflammatory, granulomatous nodules is prominent. These are characterized by the presence of large amounts of giant cells It occurs in elderly patients and the course is usually self-limited Blindness or cerebral involvement is common and the latter may result in death.

Necrotizing angiitis may also occur in association with well-defined diseases as part of the original process

Arteritis may occur in association with rheumatic fever and carditis (*rheumatic arteritis*). The small arteries and veins are involved, mainly in the myocardium and the lungs, and occasionally in the mesenteric region In any case of severe rheumatic fever, abdominal pain, renal and central nervous system involvement should lead to the consideration of a disseminated arteritis (Friedberg and Gross, 1934)

In malignant hypertension, *necrotizing arterial* [illegible] and Knowles) have found a *significant* incidence of periarteritis at necropsy in such cases Severe hypertension of the pulmonary circulation such as seen in *Eisenmenger's* syndrome (Zeek) may be associated with angiitis localized to the pulmonary *vessels* This would indicate the causative role of hypertension in a small group of cases of necrotizing *angiitis*

In all diseases of the connective tissues, angiitis may under certain circumstances exhibit an inflammatory character and resemble periarteritis nodosa Angiitis has also been described in granulomatous diseases such as Boeck's sarcoidosis (Jackson and Kass).

PROGRESSIVE SYSTEMIC SCLEROSIS (P.S.S.)

Cardiovascular involvement in P.S S. dominates the clinical picture in many cases and represents, next to the involvement of the skin, esophagus, and lungs, the most important manifestation of this disease. The histological changes occurring in the arterioles consist of thickening of the vascular walls, mainly due to adventitial fibrosis and infiltration with round cells. Proliferation of the intima is frequent and may lead to obstruction of the vessel Any artery in the body may be affected by these or similar changes, *although* the smaller arteries are involved most frequently. Along with the typical changes of the collagen bundles and the fragmentation of the elastic fibers, the vascular changes are the criterion for the histological diagnosis in biopsy material The abundance and thickening of the collagen fibers in various organs, particularly the skin, has no direct relationship to the narrowing of the vascular bed and cannot be regarded therefore as a result of ischemia Only in the kidney is there a characteristic pattern of vascular involvement (Moore and Sheehan). Here the initial lesion consists of thickening of the intima of the interlobular arteries with or without fibrinoid necrosis of the distal interlobular arteries and the afferent arterioles. Depending on the severity of these changes, the next stage may be atrophy of the renal cortex, fibrosis of the glomeruli, and even ischemic necrosis Some question has arisen whether steroid therapy in this condition may not be responsible for such renal changes.

A vascular involvement is also prominent in the clinical syndrome of P S S Raynaud's phenomenon occurs frequently and may be one of the early signs of this disease. In far-advanced cases, trophic changes of the finger tips with ulcerations may be observed

Multiple *factors* combine to result in an impairment of the pulmonary function Bronchiolar involvement, *as well* as a decrease of mobility of the chest and the diaphragm, may severely *impair* pulmonary function, leading to hypoxia and hypercapnea. In addition, vascular obliteration leads to a reduced pulmonary vascular *bed*, giving rise to pulmonary

hypertension. Other factors, such as spotty compensatory emphysema and endobronchial infection due to bronchial obstruction, further impair the physiological processes. All these changes cause a severe strain upon the right heart and may be followed by cor pulmonale.

Cardiac involvement in progressive systemic sclerosis was first adequately studied by Weiss et al and, since then, has been widely recognized (Beigelman et al; Goetz). The weight of the heart is usually increased. Hypertrophy and dilatation of the right heart is common and related to the pulmonary lesions

Pleural and pericardial thickening is frequent. The myocardial changes consist of patchy fibrosis, occasionally secondary to local ischemia due to the vascular lesions, but more frequently independent of the vascular involvement. The interstitial changes may be observed in various stages from early hyperemia and young connective tissue to actual fibrosis. Muscle fibers are destroyed and replaced by interstitial fibrosis (*scleroderma heart*)

Clinical manifestations of the cardiac involvement will vary depending on the extent of the myocardial involvement and the pulmonary disease In cases in which the myocardial involvement is extensive, congestive failure may be the outstanding manifestation and, in certain cases, precede the skin involvement. More localized or less extensive lesions may lead to disturbances in the electrical conduction, and the abnormal electrocardiogram may be the only sign of heart disease The pulmonary disease may impose a severe strain upon the right heart and the full picture of chronic cor pulmonale is quite frequently encountered in P S S Death may ensue from right heart failure The evaluation of the role of right heart failure in causing cyanosis, dyspnea, and rales, may be difficult because of the simultaneous pulmonary involvement Pleural and pericardial effusion may be on the basis of pleuritis and pericarditis, which, however, is rare in P S S. Dependent edema is quite common and may exist without congestive failure Auscultatory findings are not characteristic· accentuation of the 2d pulmonic sound, systolic murmur, gallop rhythm, poor quality of both heart sounds, or decreased intensity of the 1st sound may be encountered. Cardiac catheterization may reveal an elevated pulmonary artery pressure (Austrian et al.).

Enlargement of the pulmonary artery and right ventricle has been demonstrated by means of angiography. When examined roentgenologically, the heart may show a triangular shape with poor pulsations, resembling the findings in pericardial effusion, although pericardiocentesis yields no fluid, and cardiac enlargement is not uncommon. The electrocardiographic alterations in P S S will depend upon the extent and location of the myocardial lesions as well as the degree of pulmonary hypertension. There may be only nonspecific ST-T alterations or prolongation of the AV and intraventricular conduction time due to focal fibrosis in the myocardium The intraventricular block is usually right-sided Low voltage and arrhythmias such as atrial fibrillation and flutter have been described In advanced cases with extensive replacement of the myocardium by connective tissue (Beigelman et al.), patterns of left heart strain and of myocardial infarction may be encountered

The clinical picture of the "scleroderma kidney" is well explained by the vascular changes described above and is characterized by albuminuria, hematuria, and cylindruria The blood pressure rises within a short period of time and azotemia becomes apparent Such changes are usually late manifestations of the disease

DERMATOMYOSITIS

The clinical syndrome of dermatomyositis is dominated by the involvement of the skin and skeletal musculature. The usual onset is characterized by various forms of dermatitis, cutaneous edema, and muscle tenderness which may progress to severe atrophy and weakness, even simulating muscular dystrophy. Fever is frequently present but there are no characteristic hematologic or biochemical findings present. Urinary abnormalities are uncommon and nonspecific. An interesting fact is the high incidence of malignant neoplasms associated with dermatomyositis (Curtis et al.).

The primary pathological process is one of degeneration of muscle fibers, but there may be varying amounts of inflammatory reaction Vascular changes consist of fibrinoid necrosis and deposition of hyalinized material in the media of arterioles, as well as occasional platelet thrombi (Pagel et al.). Inflammatory reactions of the vessels are scanty but occlusions have occurred. These changes have been described in arterioles of small caliber in the

striated muscles, myocardium, and submucosal vessels of the intestinal tract (Wainger and Lever). Some of the latter have been described as being associated with necrosis and hemorrhage. Histologic alterations have been described in all elements of the myocardium Muscle fibers show fragmentation, loss of striation, and vacuolization The interstitial tissue shows swelling, edema, and occasional inflammatory infiltrates. The myocardial changes resemble those seen in the skeletal muscles but are less severe Pericarditis is rare and Aschoff's nodules are not seen

Clinically, the most prominent vascular manifestation is that of *Raynaud's phenomenon*, which may be seen in 10 to 25 per cent of cases, its presence indicates that functional as well as pathological changes are present Nephropathy and secondary hypertension are uncommon, serositis is unusual

Despite the frequency of histologic changes in the myocardium, major clinical manifestations of cardiac involvement are not prominent Findings such as tachycardia disproportionate to temperature elevation, and electrocardiographic alterations (S-T depressions and flat or inverted T waves in various leads) are common However, congestive failure, though reported, is uncommon Cardiomegaly is not common, although O'Leary and Waisman noted five instances in their series. Arrhythmias, such as auricular fibrillation and tachycardia and SA and AV block, have been observed on occasion A blowing systolic murmur may be heard in the absence of valvulitis Dyspnea is usually due to involvement of the respiratory muscles. The usual cause of death is pneumonia or respiratory failure secondary to the involvement of the muscles of deglutition and respiration Some of the aspects of this condition were recently reviewed by Domzalski and Morgan.

THE SERUM SICKNESS SYNDROME

A great deal of experimental work has been concerned with the pathologic changes occurring after injection of foreign protein, and much of our knowledge of the behavior of the cardiovascular system under such conditions has been gained from these experiments The application of this knowledge to clinical medicine, as reviewed by Ehrich, has yielded important contributions to our understanding of the serum sickness syndrome Moreover, conclusions have been drawn from such experiments in regard to collagen diseases in general The significance of antigen-antibody reactions in the production of cardiovascular changes and the hyperglobulinemia associated with these conditions have been intensely studied. Still, the gap between the acute serum-sickness type of syndrome and the self-maintained, chronic "collagen" disease remains to be filled.

The serum sickness syndrome can become manifest, not only after parenteral administration of proteins, but also after administration of smaller molecules (such as penicillin) by mouth It occurs after a latent period, probably necessary for the formation and deposition of antigen-antibody reactors in the tissues. Urticaria, joint swellings, and fever are the most prominent signs The course is self-limited, and healing occurs without residual damage to the tissues in the majority of cases. Death, however, may occur during such severe reactions Pathological studies of autopsied cases reveal extensive lesions involving the smaller vessels and all the cardiac structures. Tissue swelling and edema are seen in the early stages Fibrinoid necrosis of the vascular wall, proliferation of fibroblasts and endothelial cells, as well as infiltration with lymphocytes and plasma cells in all layers of the heart occur. Pericardial and pleural effusions have been described In milder cases, no cardiovascular manifestations may be obvious, except for abnormal capillary permeability as indicated by the urticaria In some instances, changing loud systolic murmurs and cardiac enlargement occur Electrocardiographic abnormalities have been described. They consist mainly of nonspecific ST-T changes. However, a number of instances of young individuals with electrocardiographic evidence of myocardial infarction has been reported. Pericardial friction rubs and electrocardiographic evolution of typical pericarditis have also been described (Contro and Mond)

STEROID THERAPY OF CARDIOVASCULAR COMPLICATIONS IN COLLAGEN DISEASES

Since the introduction of ACTH and the various adrenal steroids and their derivatives into clinical medicine, new avenues of therapy have been opened, and a new, intensive study of the subject from the theoretical and clinical viewpoint, has begun. So far, no proof of an

hypertension. Other factors, such as spotty compensatory emphysema and endobronchial infection due to bronchial obstruction, further impair the physiological processes. All these changes cause a severe strain upon the right heart and may be followed by cor pulmonale.

Cardiac involvement in progressive systemic sclerosis was first adequately studied by Weiss et al. and, since then, has been widely recognized (Beigelman et al.; Goetz). The weight of the heart is usually increased. Hypertrophy and dilatation of the right heart is common and related to the pulmonary lesions.

Pleural and pericardial thickening is frequent The myocardial changes consist of patchy fibrosis, occasionally secondary to local ischemia due to the vascular lesions, but more frequently independent of the vascular involvement The interstitial changes may be observed in various stages from early hyperemia and young connective tissue to actual fibrosis Muscle fibers are destroyed and replaced by interstitial fibrosis (*scleroderma heart*)

Clinical manifestations of the cardiac involvement will vary depending on the extent of the myocardial involvement and the pulmonary disease. In cases in which the myocardial involvement is extensive, congestive failure may be the outstanding manifestation and, in certain cases, precede the skin involvement More localized or less extensive lesions may lead to disturbances in the electrical conduction, and the abnormal electrocardiogram may be the only sign of heart disease. The pulmonary disease may impose a severe strain upon the right heart and the full picture of chronic cor pulmonale is quite frequently encountered in P.S S Death may ensue from right heart failure The evaluation of the role of right heart failure in causing cyanosis, dyspnea, and rales, may be difficult because of the simultaneous pulmonary involvement Pleural and pericardial effusion may be on the basis of pleuritis and pericarditis, which, however, is rare in P.S S. Dependent edema is quite common and may exist without congestive failure Auscultatory findings are not characteristic· accentuation of the 2d pulmonic sound, systolic murmur, gallop rhythm, poor quality of both heart sounds, or decreased intensity of the 1st sound may be encountered. Cardiac catheterization may reveal an elevated pulmonary artery pressure (Austrian et al).

Enlargement of the pulmonary artery and right ventricle has been demonstrated by means of angiography. When examined roentgenologically, the heart may show a triangular shape with poor pulsations, resembling the findings in pericardial effusion, although pericardiocentesis yields no fluid, and cardiac enlargement is not uncommon. The electrocardiographic alterations in P.S S will depend upon the extent and location of the myocardial lesions as well as the degree of pulmonary hypertension. There may be only nonspecific ST-T alterations or prolongation of the AV and intraventricular conduction time due to focal fibrosis in the myocardium The intraventricular block is usually right-sided Low voltage and arrhythmias such as atrial fibrillation and flutter have been described. In advanced cases with extensive replacement of the myocardium by connective tissue (Beigelman et al), patterns of left heart strain and of myocardial infarction may be encountered

The clinical picture of the "scleroderma kidney" is well explained by the vascular changes described above and is characterized by albuminuria, hematuria, and cylindruria The blood pressure rises within a short period of time and azotemia becomes apparent Such changes are usually late manifestations of the disease

DERMATOMYOSITIS

The clinical syndrome of dermatomyositis is dominated by the involvement of the skin and skeletal musculature The usual onset is characterized by various forms of dermatitis, cutaneous edema, and muscle tenderness which may progress to severe atrophy and weakness, even simulating muscular dystrophy Fever is frequently present but there are no characteristic hematologic or biochemical findings present. Urinary abnormalities are uncommon and nonspecific An interesting fact is the high incidence of malignant neoplasms associated with dermatomyositis (Curtis et al.).

The primary pathological process is one of degeneration of muscle fibers, but there may be varying amounts of inflammatory reaction Vascular changes consist of fibrinoid necrosis and deposition of hyalinized material in the media of arterioles, as well as occasional platelet thrombi (Pagel et al.). Inflammatory reactions of the vessels are scanty but occlusions have occurred. These changes have been described in arterioles of small caliber in the

triated muscles, myocardium, and submucosal vessels of the intestinal tract (Wainger and Lever). Some of the latter have been described as being associated with necrosis and hemorrhage Histologic alterations have been described in all elements of the myocardium Muscle fibers show fragmentation, loss of striation, and vacuolization The interstitial tissue shows swelling, edema, and occasional inflammatory infiltrates The myocardial changes resemble those seen in the skeletal muscles but are less severe Pericarditis is rare and Aschoff's nodules are not seen.

Clinically, the most prominent vascular manifestation is that of *Raynaud's phenomenon*, which may be seen in 10 to 25 per cent of cases, its presence indicates that functional as well as pathological changes are present Nephropathy and secondary hypertension are uncommon, serositis is unusual

Despite the frequency of histologic changes in the myocardium, major clinical manifestations of cardiac involvement are not prominent Findings such as tachycardia disproportionate to temperature elevation, and electrocardiographic alterations (S-T depressions and flat or inverted T waves in various leads) are common. However, congestive failure, though reported, is uncommon Cardiomegaly is not common, although O'Leary and Waisman noted five instances in their series Arrhythmias, such as auricular fibrillation and tachycardia and SA and AV block, have been observed on occasion A blowing systolic murmur may be heard in the absence of valvulitis Dyspnea is usually due to involvement of the respiratory muscles. The usual cause of death is pneumonia or respiratory failure secondary to the involvement of the muscles of deglutition and respiration Some of the aspects of this condition were recently reviewed by Domzalski and Morgan.

THE SERUM SICKNESS SYNDROME

A great deal of experimental work has been concerned with the pathologic changes occurring after injection of foreign protein, and much of our knowledge of the behavior of the cardiovascular system under such conditions has been gained from these experiments The application of this knowledge to clinical medicine, as reviewed by Ehrich, has yielded important contributions to our understanding of the serum sickness syndrome. Moreover, conclusions have been drawn from such experiments in regard to collagen diseases in general The significance of antigen-antibody reactions in the production of cardiovascular changes and the hyperglobulinemia associated with these conditions have been intensely studied. Still, the gap between the acute serum-sickness type of syndrome and the self-maintained, chronic "collagen" disease remains to be filled.

The serum sickness syndrome can become manifest, not only after parenteral administration of proteins, but also after administration of smaller molecules (such as penicillin) by mouth It occurs after a latent period, probably necessary for the formation and deposition of antigen-antibody reactors in the tissues. Urticaria, joint swellings, and fever are the most prominent signs The course is self-limited, and healing occurs without residual damage to the tissues in the majority of cases Death, however, may occur during such severe reactions Pathological studies of autopsied cases reveal extensive lesions involving the smaller vessels and all the cardiac structures. Tissue swelling and edema are seen in the early stages Fibrinoid necrosis of the vascular wall, proliferation of fibroblasts and endothelial cells, as well as infiltration with lymphocytes and plasma cells in all layers of the heart occur Pericardial and pleural effusions have been described. In milder cases, no cardiovascular manifestations may be obvious, except for abnormal capillary permeability as indicated by the urticaria. In some instances, changing loud systolic murmurs and cardiac enlargement occur. Electrocardiographic abnormalities have been described They consist mainly of nonspecific ST-T changes However, a number of instances of young individuals with electrocardiographic evidence of myocardial infarction has been reported Pericardial friction rubs and electrocardiographic evolution of typical pericarditis have also been described (Contro and Mond).

STEROID THERAPY OF CARDIOVASCULAR COMPLICATIONS IN COLLAGEN DISEASES

Since the introduction of ACTH and the various adrenal steroids and their derivatives into clinical medicine, new avenues of therapy have been opened, and a new, intensive study of the subject from the theoretical and clinical viewpoint, has begun. So far, no proof of an

actual cure in any of the disorders is available, although the beneficial results in certain cases are striking.

Steroid therapy improves the patient's subjective sense of well-being. The fever, the joint, skin, mucous membrane, and other manifestations respond dramatically in many cases. The plasma proteins and the hematological manifestations may revert towards normal. The effects of these substances on the actual pathohistology in S.L.E. is poorly understood. Serial renal biopsies do not seem to contribute to our knowledge of the influence of corticoids upon the basic lesion. Autopsies of cases of S.L.E. treated with steroids or ACTH do not seem to reveal any major differences from untreated cases. It must be remembered, though, that clinically well-documented cases of S.L.E., which at autopsy showed none of the pathological changes expected, have been repeatedly described. The endocarditis characteristic of S.L.E. does not seem to be influenced by ACTH or the corticoids. The pericarditis and pericardial effusion may disappear. The influence on the myocarditis may be favorable, with decrease in heart size and subsidence of congestive failure.

Necrotizing angiitis is in general favorably influenced by the administration of ACTH or steroids. Actual healing can be observed histologically but may result in occlusion of vessels, this may lead to serious complications (Shick and Kvale).

Theoretical considerations indicate that corticosteroids have a profound effect upon the function and structure of small blood vessels and could lead to actual angiitis through an obscure mechanism (Taubenhaus et al.). Angiitis may also occur if there is an abrupt withdrawal of corticoids after a period of prolonged therapy (Slocumb et al.)

The cardiovascular manifestations of progressive systemic sclerosis are not significantly influenced by steroid therapy, although some beneficial effects upon the cutaneous manifestations, the esophagus, and to a certain degree the pulmonary lesions has been described (Taubenhaus et al.).

In dermatomyositis there may be a favorable effect upon the general symptom pattern, but insufficient information exists concerning the effect upon cardiovascular manifestations.

Serum sickness is a self-limited disease, the duration and severity of which may be favorably influenced by steroid therapy.

CORTICAL STEROIDS AND COLLAGEN DISEASES

With the demonstration of the effectiveness of adrenal corticoids and ACTH in collagen diseases, two important questions have arisen.

1. Are collagen diseases actually associated with or caused by endocrine disorders, in particular adrenocortical deficiency?

2. What is the mode and mechanism of the action of corticoids?

The answer to the first question is that there is no evidence that endocrine disease is pathogenetically related to collagen diseases. All the endocrine manifestations described can be encountered in any other chronic disease and are related to stress and exhaustion of the endocrine system. Extensive literature has accumulated dealing with the mode of action of anti-inflammatory steroids. In general, it can be said that at least three factors play an important role:

1. An altered vascular reaction to allergic and inflammatory processes resulting in alteration of the course and reduced formation of new capillaries in granulation tissue.

2. A suppression of all the mesenchymal structures playing a major part in inflammatory and allergic conditions. This suppression includes the fibroblasts, ground substance, and collagen fibers, which are all constituents of the tissues affected in collagen diseases.

3. Information has also accumulated that steroids interfere with the formation of antibodies and certain antibody-antigen reaction

THE HEART IN LUPUS ERYTHEMATOSUS; THE HEART IN LIBMAN-SACKS DISEASE

The frequency with which the heart is involved clinically, pathologically, or both, in lupus, is well documented and has been emphasized in several monographs (Talbott; Harvey et al.). A figure of at least 50 per cent would seem conservative.

Historically, the cardiac manifestations were described by Osler (1895), who stressed the

visceral complications including instances involving the heart in particular, and the cardiovascular system in general His original impressions have been analyzed and reevaluated by many others, particularly Tumulty and Harvey, and again by the Reifensteins Libman and Sacks (1924) stressed the endocardial factor and described in detail the pericardial and myocardial involvement. Baehr and Klemperer and Schifrin also reviewed the problem extensively, as have many others

The "rediscovery" (to use Talbott's term) of this interesting syndrome as a collagen disease is probably due to improved methods and techniques of L E cell demonstration and to other diagnostic procedures Dubois (1956) pleads for an awareness of the disease on the grounds that he has seen 175 patients in 6 years in one hospital, an incidence making the entity more common than subacute bacterial endocarditis, leukemia, pernicious anemia, or Hodgkin's disease—at least in that institution

The sex distribution is *predominantly female*, on the order of at least 90 per cent Detailed studies as to causative factors have been focused on physical, chemical, and bacteriologic aspects and, in the last, both tubercular and streptococcic origin have been suggested The relationship to other so-called collagen diseases has been reviewed by Talbott, and the differential diagnosis is concerned with such entities as rheumatoid arthritis, acute rheumatic fever, Raynaud's syndrome, polyarteritis, dermatomyositis, scleroderma, and thrombocytopenic purpura.

PATHOLOGIC CHARACTERISTICS

Lupus is a complex multiorgan-system disease, in which the heart may be extensively involved *Gross* (1940), in his evaluation of data supplied by others, noted nonbacterial, verrucous endocarditis in 55 per cent of the cases, sometimes the plaques are small, often they are large and flat Pericardial involvement occurred in 70 per cent of the cases, either by serous effusion or adhesive pericarditis. Myocardial involvement occurred in 35 per cent, the myocardial process may be intrinsic or due to vascular changes in the coronary system Capillaries, arterioles, and venules are involved and ...

ground substance and collagen fibers has been noted. Subendothelial necrosis may be present, with minimal evidence of overlying endocarditis. Hematoxylin-staining bodies have been found in the cardiac lesions at autopsy.

Dr. Terplan[1] has compiled for the author the gross and microscopic data on three typical cases. It is his feeling, and that of the author's clinical group that there is little evidence to support the theory of relationship to rheumatic lesions, the tissue reactions being of a different nature. On the other hand, there is much to support the theory of embolic phenomena. The author's cases also *emphasize the diffuseness* of the involvement throughout the epicardium, myocardium, and endocardium Three cases studied from the standpoint of gross and microscopic pathology follow.

No. 8591 C.W., 45, April 9, 1954

Gross Examination. The pericardial sac is adherent throughout, by fibrous bands, to the epicardium. The heart is normal in size On section, the myocardium is pale The tricuspid and pulmonic valves are normal, the mitral valve shows marked fibrous thickening A few pinhead-sized elevations are present on the mitral leaflets. The chordae tendineae are markedly thickened, the papillary muscles of the left ventricle show fibrosis. The aortic cusps are fused at the commissures in two areas The valves measure as follows: tricuspid, 11 cm, pulmonic, 7 cm, mitral, 10 5 cm, aortic, 8 cm The right ventricle measures 6 cm in thickness, the left 2 cm. The coronary arteries are patent throughout, with minimal atheromatosis in their walls

Histologic Findings. LEFT ATRIUM. There is a very distinct thickening of the endocardium, with edema and comparatively slight new formation of collagenous fibers There is distinct edema throughout the myocardium with the individual fibers distinctly separated by tissue fluid, there is only minimal activation of histiocytes. Distinct thickening of the en...

... near the surface Some fibrinoid degeneration can also be seen in other parts of the epicardium, especially in the deeper portions close to the myocardium

LEFT VENTRICLE Similar changes appear in the epicardium, with scattered lymphocytes and increase of capillaries. There are also a few fair-

[1] Professor of Pathology, University of Buffalo, School of Medicine

sized histiocytes, but no *Aschoff nodules.* Some fibrinoid change is seen close to the attachment of the heart muscle as well as very conspicuous thickening of the attached valve, with localized edema, pseudocystic liquefaction, and irregular fibrous thickening of the endocardium on the surface of the valve. Other parts are firmly collagenized and show minimal spotty deposits of calcium. There are very prominent fibrocytes, especially around the more edematous pseudocystic areas. The changes described are seen predominantly in the mitral valve

LEFT VENTRICLE AT THE ATTACHMENT OF THE AORTIC LEAFLET There are extensive changes in the epicardium, just as described, with distinct capillarization and edema Also present are typical chronic inflammatory changes, formed largely by histiocytes, a few round cells, edema fluid, and young fibroblasts There is older fibrinoid change in the endocardium of the aortic valve, but only moderate hyalinization. There are rather large areas with granular degeneration of the ground substance, staining somewhat more intensely and slightly purplish with eosin Only scattered proliferating histiocytes are seen at the border of the attached epicardium and myocardium.

RIGHT ATRIUM The most impressive changes are in the epicardium, namely, conspicuous fibrinoid degeneration and rather marked chronic inflammatory reaction together with marked vascularization, edema, and proliferation of histiocytes and fibroblasts, along with a few leucocytes surrounding the fibrinoid precipitations (Fig 16-4). Part of this exudate, in the process of organization, is infiltrated by numerous young fibroblasts, few lymphocytes, and very few leucocytes. These changes are quite extensive. In contrast, there is only minimal edema and slight activation of fibrocytes, with few round cells in the interstitial tissue of the myocardium, which is distinctly edematous. There is slight leucocytic infiltration in a focal distribution in some fibers of the myocardium closer to the endocardium, which also shows edema and activation of fibrocytes.

RIGHT VENTRICLE. This chamber reveals similar changes in the epicardium, with unusually marked edema but more lymphocytic infiltration and activation of histiocytes and young fibroblasts There is distinct extension of this edema and inflammatory reaction into the interstitial tissue of the myocardium, with prominent proliferation of histiocytes, although there is no actual formation of nodular structures. *These infiltrations* show the typical morphology of the so-called *Anitschkow cells* There is, in general, distinct proliferation of fibroblasts between individual myocardial fibers

There are no changes in the *coronary artery,* except for very minimal edema, with slight hyalinization in the inner media. In some areas of the left ventricle, the inflammatory reaction is more conspicuous than in others within the epicardium. Again there is marked activation of both fibroblasts

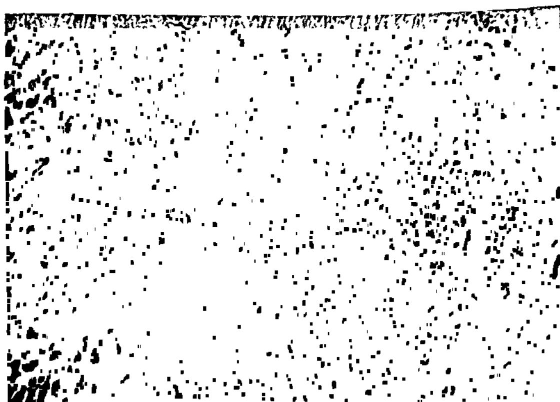


Fig. 16-4. Histologic section of right atrium.

ıd histiocytes in the interstitial tissue of the myo-ardium

The striated musculature showed the most severe hanges of chronic myositis and very marked simi-ır changes in the surrounding fascia and the deep ubcutaneous tissue.

No. 9609 R S, 27, September 17, 1956

Gross Examination. The pericardial sac contains blood-tinged fluid amounting to about 100 ml A delicate film of yellowish-gray fibrinous exudate is seen on the superior anterior surface of the left ventricle, aorta, and pulmonary artery, resulting in an opaque thin sheen covering the epicardium, which otherwise is thin and glistening above the remaining portions of the heart The myocardium of the right ventricle measures 0 4 cm in thickness, the left ventricle, 2 5 cm, the latter shows concentric muscular hypertrophy and fibrotic changes on the posterior wall The trabeculae carneae and papillary muscles are hypertrophied, round, and sturdy, presenting whitish areas of fibrosis, suggestive of embolic phenomena The right ventricle appears dilated with an increased design of moderately prominent trabeculae carneae, suggesting a cor pulmonale The foramen ovale is closed The measurements of the valves are as follows: aortic, 9 cm, pulmonic, 10 cm, mitral, 10 cm, and tricuspid, 12 cm There is an endocarditic change in the mitral valve, characterized by formation of irregular verrucae, giving the gross appearance of *Libman-Sacks disease* The endocarditic vegetations are arranged in conglomerates of mulberry-like masses, localized over the atrial surface of the posterior leaflet, approximately at the margin of the valve attachment The *verrucae* have a tawny yellow color and are of rather soft consistency The aortic valve, also, shows verrucous formations, consisting of a single, beadlike chain along the closing edges, as seen in old remnants of valvular endocarditis.

Histologic Findings MITRAL VALVE. There are very distinct verrucous vegetations, consisting mostly of collagenous fibers. Only close to the surface is there some irregular edema and slight mucoid degeneration Other parts show a very firm, almost entirely hyalinized center Between the small verrucous protrusions, there is older granulation tissue with a few capillaries and localized infiltration by fibroblasts and a few lymphocytes In addition, there are more recent vegetations on the surface, consisting largely of fibrinoid precipitations, firmly adherent and only in the deeper portions partly organized There are a few hemosiderin granular cells close to this area

MYOCARDIUM No inflammatory changes are seen, and there is only slight edema There is distinct hypertrophy of the individual muscle fibers and a few older small fibrous scars, with edema of rather large areas of the original myocardium These changes are present throughout most of the myocardium of the left ventricle Other sections of the left ventricle, particularly of the septum, show extensive older scars in the myocardium, but there is some cellular infiltration along the borders of these scars by histiocytes and fibroblasts, with some *capillarization.*

No 8568 A.B., 66, March 19, 1954 (Case of Cancer)

Gross Examination. The pericardium contains a small amount of straw-colored fluid. The heart is not enlarged and its chambers are of normal size and thickness The right myocardium measures 3 5 mm in thickness and the left, 10 to 15 mm The mitral valve has small fibrinous vegetations along its closing edge, suggesting a recent verrucous valvular endocarditic change. There is no scarring or calcification present Its circumference is 10.5 cm The remaining valves are normal and measure respectively: tricuspid, 12 5 cm, pulmonary, 8 5 cm, and aortic, 7 5 cm. The coronary arteries are fairly smooth and of good caliber

Histologic Findings. There are a few older small scars in the myocardium, especially in the papillary muscles Also, there is slight edema. In addition, firmly attached recent thrombi are seen between the trabeculae. Other sections show extensive older scarring in the myocardium together with numerous hemosiderin cells and with hypertrophy of the surrounding muscle fibers, representing small old infarct-like changes The epicardium is not involved, except for infiltration by cancer cells and edema There are no remarkable changes in the right ventricular myocardium, except for infiltration by fat tissue

The *heart valves* present distinct formations of small *verrucous protrusions* with considerable hyalinization and some mucoid degeneration of the thickened endocardium There is a firmly adherent fibrinoid exudate, partly organized and containing comparatively few leucocytes, this is distinctly liquefied in its basal attachment to the endocardium There are no specific rheumatic nodules.

CLINICAL PICTURE

The systemic picture includes fever, progressive anemia, pericarditis, white-centered petechiae, erythematous and purpuric rashes, embolic phenomena, enlarged liver and spleen, and other manifestations. It may well be *subacute* but occasionally there are alarming *acute episodes,* many of which involve the cardiovascular system. The physical signs from a cardiac standpoint are often difficult to evalu-

ate. The *systolic murmur* may be misinterpreted because of the presence of fever, anemia, and tachycardia. *Diastolic murmurs* may occur when verrucae involve the valve cusps or large lesions spread to the chordae tendineae. *Pericarditis,* usually dry and fibrinous (occasionally effusive) causes friction rubs which are frequently heard. Myocarditis, cardiomegaly, hypertension, cardiac failure, arrhythmia, and electrocardiographic evidence of conduction defects may occur in this order of frequency By the same token, the physical findings and clinical signs will depend upon the dominant complicating cardiac or cardiovascular involvement. The systolic murmur is nonspecific in character and distribution; the diastolic murmur, if present, could simulate the rumble of rheumatic mitral stenosis. The dry type of pericardial involvement may result in friction rubs, the effusive type may range from absence of signs to the evidences of *tamponade* Gallop rhythm and T-wave changes in the electrocardiogram have been accepted as evidences of myocarditis. Physical and radiographic evidence of cardiac enlargement and pulmonary congestion may be present. Shortness of breath, cough, rales, liver engorgement, and peripheral edema may occur. Disturbances of the heart rate and rhythm include sinus tachycardia, premature contractions, first and second degree AV block, and atrial fibrillation The disparity, so often present, between the clinical manifestations and the demonstrable pathologic changes at autopsy has been stressed by Griffith and Vural. When tachycardia occurs, it is out of proportion to the temperature rise. However, it should be kept in mind that lupus erythematosis can be superimposed on other cardiac processes including subacute bacterial endocarditis Dyspnea and other evidence of failure may be the result of direct myocardial damage or of involvement of the coronary vessels.

DIAGNOSIS

As has been suggested, the critical physician should always suspect this disease in atypical symptom complexes which often may include cardiac disturbances. The other processes involving the collagen tissues must always be considered because, as mentioned above, rheumatoid arthritis and acute rheumatic carditis share with lupus similar laboratory findings, short of an actual demonstration of the L E cell. A few rule-of-thumb distinctions may be mentioned at this point. White-centered petechiae do not tend to occur in rheumatic endocarditis Pericarditis seldom occurs in subacute bacterial endocarditis. Biopsy should rule out periarteritis in most instances Blood cultures will confirm acute or subacute bacterial endocarditis, and serum agglutinations give positive data in tularemia and in typhoid, paratyphoid, and undulant fevers. Uremic pericarditis may have to be ruled out.

TREATMENT

As concerns the cardiac factors in systemic lupus, the treatment differs little from that of heart failure or arrhythmia in other circumstances. Although cardiac failure is not considered a contraindication to hormone therapy, more careful sodium restriction is necessary when this course is taken. Digitalis and mercurials are used as in other types of congestive heart failure. Adequate rest is very important in the presence of cardiac involvement In regard to hormone treatment, it may be difficult to determine whether the failure is due to steroid therapy or to the progression of the disease *Prednisone,* in doses of 20 to 40 mg daily, seems the drug of choice because it has less sodium-retaining activity than other steroids. Supplementary use of oral or parenteral diuretics and potassium is helpful in maintaining water and electrolyte equilibrium As noted by Talbott and Ferrandis, there is no statistical evidence to date that steroid therapy affects the basic process underlying the disease, but there is overwhelming evidence that there is considerable symptomatic relief for variable periods of time. Therefore, congestive heart failure should not be considered as a reason for withholding this type of therapy.

4

The heart in glycogen disease

ISADORE SNAPPER

In 1927 van Creveld and Snapper studied a 7-year-old boy with a large liver, hypoglycemia, and acetonuria, but no splenomegaly. An exploratory laparotomy had been performed when the child was 8 months old because of progressive enlargement of the abdomen. At that time, the only finding was a large and soft liver which grossly gave the impression of being a fatty liver. Unfortunately, no biopsy had been performed.

During the admission in 1927, this child had marked hypoglycemia and acetonuria in the morning, together with a marked increase of the ketone bodies (both acetone and beta-hydroxybutyric acid) in the blood. During the blood sugar tolerance test, a biphasic blood sugar curve was obtained without the development of any clinical symptoms or signs of hypoglycemia. In the presence of acetonuria and acetonemia, the hypoglycemia could not be caused by either an insulinoma or a widespread hepatoma. Therefore the author considered the possibility that in this child the glycogen depots in the liver, probably also in the muscles, could not be transformed into glucose. This explanation was supported by the finding that injection of 0.5 mg of epinephrine, which in normal children causes hyperglycemia, was followed by a negligible rise in the blood sugar. In addition, after the injection, this child excreted a markedly increased quantity of acetone and beta-hydroxybutyric acid. In normal subjects, the metabolism of carbohydrates increases under the influence of an injection of epinephrine. Consequently, the respiratory quotient goes up and ultimately approaches unity. In the author's patient epinephrine had an opposite influence and the respiratory quotient decreased. The lowering of the respiratory quotient indicates an increase of the combustion of fats, another point which favored the opinion that glycogen was not available as a source of calories. This was later confirmed by the observation that, in similar cases, epinephrine does not cause a rise in the lactic-acid content of the blood, as it does in normal individuals.

One year later, von Gierke (1929) reported the autopsies of two children with large liver and large kidneys, in whom the enlargement of these organs was caused by an accumulation of glycogen. Since the glycogen, as determined by Schoenheimer, persisted in these organs for several days after the autopsy had been performed, von Gierke concluded that the glycogen must have been abnormal and must have been much less sensitive to enzymatic action than normal glycogen.

For many years van Creveld had pursued the study of the problems of glycogen disease. His follow-up of the first patient is highly interesting. Although, in 1927, this child gave the impression of suffering from an adiposogenital syndrome, he has developed into a normal man who, at the age of 30, was 1.83 m tall and weighed 89 kg. He had married and had a son. The liver was just palpable. The skeletal development was completely normal, although during his childhood delayed ossification had been present. The fasting blood sugar was completely normal and acetonuria was absent. Nevertheless—as was the case 23

years previously—after an injection of epinephrine, the blood sugar did *not* increase. However, the acetonuria was only slight. Van Creveld observed the same favorable course of events in a girl with glycogen disease of the liver. He first studied this patient when she was 5 years old and followed her until she reached the age of 24 years

Since Amsterdam is the place where glycogenosis of the liver was first recognized as a disease entity, it is no wonder that another form of glycogen disease, the so-called *cardiac or generalized type of glycogen storage disease,* was also first observed and described in the same city. In 1930 a 7-month-old girl was admitted to the hospital. She had a normal development and had been healthy until a few days before admission, when dyspnea had started. The child appeared sick, with a pale-cyanotic skin, sunken eyes, and severe dyspnea The heart appeared normal on percussion but the heart sounds were muffled Signs of pneumonia were present in the left lower pulmonary lobe. The child died 4 days later. The autopsy was performed by Pompe, who found a tremendously large and globular heart. The apex of the heart was formed by both ventricles. All valves were normal and no abnormal shunts were present The musculature of the left ventricle was hypertrophied and measured 29 mm without trabeculae The right ventricle measured 9 mm These figures should be compared with those of 7 to 10 mm for the left ventricle, and 2 to 5 mm for the right ventricle in an adult male. The coronary arteries were normal. There was bilateral bronchopneumonia, more pronounced at the left. Liver, spleen, adrenals, kidneys, and all other organs, were grossly normal

A diagnosis of "idiopathic hypertrophy of the heart" was made. However, two days later the heart muscle was examined in frozen sections, and the myocardium proved to consist of a network of round and oval meshes in which a nucleus, either in the middle of the cavity or at the lateral walls, was often found. It soon appeared that this remarkable picture, the so-called *lace-work appearance,* was due to a vacuolar change of the muscle fibers of the heart. In these changed fibrils, no fat was found Pompe felt that these abnormal fibrils were similar to the fibers of Purkinje He therefore examined the heart for the presence of glycogen and found that large amounts of glycogen were present in the heart muscle, and in all other organs.

Pompe insisted that this disease represents a glycogen infiltration of practically all organs. He also emphasized that, in the disease which now is called von Gierke's disease, the abnormal glycogen is present only in the enlarged liver and kidneys, not in the other organs, especially not in the heart. Pompe proposed for the disease he described the name of "cardiomegalia glycogenica," or, as he preferred, "glycogen depository disease." Pompe remarked that in the future, in every case of hypertrophy and dilatation of the heart without a clear-cut origin, the possibility of a glycogen heart must be considered. The diagnosis of generalized glycogenosis is much more difficult than the recognition of the hepatic form of glycogen disease. The metabolic changes which characterize the latter disease are absent in the cardiomegalic form. Only a muscle biopsy will reveal the presence of the generalized form of glycogen disease.

The clinical picture caused by the glycogen heart disease is nearly always the same as that described in Pompe's first patient, i e, attacks of dyspnea and cyanosis in a child with an enlarged heart. In a few cases heart murmurs have been heard. Malnutrition was nearly always present. At roentgenographic examination, the cardiac enlargement usually gave rise to a globular shaped shadow of the heart Electrocardiographic anomalies have been observed in several cases, but these changes can hardly be considered characteristic. The disease has been reported in siblings

All these children have succumbed below the age of 1 year. The gross pathologic and histologic changes in all cases were identical with the ones originally described by Pompe Retardation of the disappearance of the glycogen deposited in the different organs was nearly always present.

For the differential diagnosis, diffuse rhabdomyomatosis of the heart must be considered A few other cases of *focal* glycogen infiltration of the heart muscle have been described, in these the blood supply to the myocardium had suffered because of congenital anomalies of the blood vessels In cases of glycogen disease of the heart, biopsy of a skeletal muscle, as mentioned above, reveals an excessive deposition

of glycogen. In some cases, an increased glycogen content of the blood and even of the leucocytes has been found.

The disease is rare, so that by 1950 only 15 proved cases could be collected from the literature.

Neither the clinical picture, the roentgenogram of the heart, nor the electrocardiogram have contributed to a better understanding of the origin of the glycogen heart. In contrast, the study of the underlying biochemical anomalies of this disease has cleared up many problems. In 1928 it seemed possible that inhibition of the action of the diastatic enzymes could be responsible for the delayed degradation of glycogen to glucose. However, studies of the structure of the glycogen molecule and isolation of the enzymes which bring about the synthesis and the degradation of glycogen have proved that these enzymes are not responsible for glycogen disease.

The multibranched structure of the glycogen molecule is of great importance to a better understanding of the glycogen disease, because several different enzymes are required to build up this complicated molecule and also to change glycogen to glucose. Just as the favorable prognosis of the liver-kidney variety of the glycogen disease is completely different from the unfavorable outlook of the glycogen heart, so are the biochemical anomalies completely different. The structure of the glycogen found in the liver-kidney glycogen disease, is within the normal range. However, one specific enzyme, glucose-6-phosphatase, is absent in the liver and kidney of these patients. The normal enzymatic degradation of glycogen is prevented, and accumulation of abnormally stable glycogen in liver and kidney results.

In all cases of generalized glycogenosis, especially in the heart-storage disease, the glucose-6-phosphatase activity is normal. However, in some of these patients the so-called debranching and branching enzyme, i.e., amylo-1,6-glucosidase, is absent. This enzyme removes the branching chains which sprout out from the central core of the glycogen molecule and also synthesizes the branching chains to the central molecule. As a result, in the heart-storage disease, the outer branches of the glycogen molecule may be abnormally short and the degradation of this abnormal molecule is impaired. When this is the case, an abnormal, short-branched glycogen molecule accumulates in the tissues of the body, especially in the heart, and remains intact for many days after death.

It is certain that other biochemical varieties of this generalized glycogen disease exist. In certain cases, the glycogen molecules were normal in configuration and had outer branches of normal length. In some of these children, the amylo-1,6-glucosidase action was normal, but the enzyme activity was very low in at least one case.

It follows that many detailed problems still have to be worked out.

SUMMARY

The so-called *glycogen heart* is a modality of generalized glycogen storage disease. In the cardiac form of glycogenosis, glycogen is deposited in many tissues, but especially in the myocardium. All patients with glycogen heart have died below the age of 1 year, usually with attacks of dyspnea and cyanosis. The heart is always enlarged. This disease has no characteristic roentgenographic or electrocardiographic signs.

A favorable prognosis and characteristic changes in metabolism differentiate the liver-kidney form of glycogenosis from the so-called glycogen heart. It has now been shown that, in the liver-kidney form, the glycogen is normal but one specific enzyme, glucose-6-phosphatase, is absent. In certain cases of the cardiac form of the general storage disease, another enzyme, amylo-1,6-glucosidase, is absent and the structure of the glycogen molecule is abnormal. This difference is of basic importance for prognosis.

years previously—after an injection of epinephrine, the blood sugar did *not* increase. However, the acetonuria was only slight. Van Creveld observed the same favorable course of events in a girl with glycogen disease of the liver. He first studied this patient when she was 5 years old and followed her until she reached the age of 24 years.

Since Amsterdam is the place where glycogenosis of the liver was first recognized as a disease entity, it is no wonder that another form of glycogen disease, the so-called *cardiac or generalized type of glycogen storage disease*, was also first observed and described in the same city In 1930 a 7-month-old girl was admitted to the hospital. She had a normal development and had been healthy until a few days before admission, when dyspnea had started. The child appeared sick, with a pale-cyanotic skin, sunken eyes, and severe dyspnea. The heart appeared normal on percussion but the heart sounds were muffled. Signs of pneumonia were present in the left lower pulmonary lobe. The child died 4 days later. The autopsy was performed by Pompe, who found a tremendously large and globular heart. The apex of the heart was formed by both ventricles. All valves were normal and no abnormal shunts were present. The musculature of the left ventricle was hypertrophied and measured 29 mm without trabeculae. The right ventricle measured 9 mm These figures should be compared with those of 7 to 10 mm for the left ventricle, and 2 to 5 mm for the right ventricle in an adult male The coronary arteries were normal There was bilateral bronchopneumonia, more pronounced at the left. Liver, spleen, adrenals, kidneys, and all other organs, were grossly normal

A diagnosis of "idiopathic hypertrophy of the heart" was made However, two days later the heart muscle was examined in frozen sections, and the myocardium proved to consist of a network of round and oval meshes in which a nucleus, either in the middle of the cavity or at the lateral walls, was often found It soon appeared that this remarkable picture, the so-called *lace-work appearance*, was due to a vacuolar change of the muscle fibers of the heart. In these changed fibrils, no fat was found. Pompe felt that these abnormal fibrils were similar to the fibers of Purkinje He therefore examined the heart for the presence of glycogen and found that large amounts of glycogen were present in the heart muscle, and in all other organs.

Pompe insisted that this disease represents a glycogen infiltration of practically all organs. He also emphasized that, in the disease which now is called von Gierke's disease, the abnormal glycogen is present only in the enlarged liver and kidneys, not in the other organs, especially not in the heart. Pompe proposed for the disease he described the name of "cardiomegalia glycogenica," or, as he preferred, "glycogen depository disease." Pompe remarked that in the future, in every case of hypertrophy and dilatation of the heart without a clear-cut origin, the possibility of a glycogen heart must be considered. The diagnosis of generalized glycogenosis is much more difficult than the recognition of the hepatic form of glycogen disease. The metabolic changes which characterize the latter disease are absent in the cardiomegalic form Only a muscle biopsy will reveal the presence of the generalized form of glycogen disease.

The clinical picture caused by the glycogen heart disease is nearly always the same as that described in Pompe's first patient, i e., attacks of dyspnea and cyanosis in a child with an enlarged heart. In a few cases heart murmurs have been heard. Malnutrition was nearly always present. At roentgenographic examination, the cardiac enlargement usually gave rise to a globular shaped shadow of the heart Electrocardiographic anomalies have been observed in several cases, but these changes can hardly be considered characteristic. The disease has been reported in siblings

All these children have succumbed below the age of 1 year. The gross pathologic and histologic changes in all cases were identical with the ones originally described by Pompe Retardation of the disappearance of the glycogen deposited in the different organs was nearly always present.

For the differential diagnosis, diffuse rhabdomyomatosis of the heart must be considered A few other cases of *focal* glycogen infiltration of the heart muscle have been described, in these the blood supply to the myocardium had suffered because of congenital anomalies of the blood vessels. In cases of glycogen disease of the heart, biopsy of a skeletal muscle, as mentioned above, reveals an excessive deposition

paramyloidosis, of the tongue causes macroglossia, of the heart, myocardial failure; of the larynx, difficulties in speech, of the esophagus, difficulties in swallowing, of the gastrointestinal tract, gastric and intestinal hemorrhages, of the subcutaneous tissue, waxy, often hard, subcutaneous masses and also, sometimes, alopecia, of the lymph nodes, lymphadenopathy; of the pulmonary tissue, dyspnea and remarkable roentgenographic pictures Amyloid deposition in the bone marrow is usually found only at a bone-marrow puncture.

As the location and the tinctorial characteristics of this form of amyloidosis differ from that which develops after suppuration, it is advisable to designate it paramyloidosis The term primary amyloidosis, often used, is hardly appropriate since this form only rarely occurs in the absence of a clear-cut origin.

There is one localization which is characteristic of paramyloidosis in patients with multiple *myeloma* In the latter disease, paramyloid is often localized on the synovial capsules of the articulations, whereas this is rare in patients who do not suffer from multiple myeloma

In paramyloidosis, liver, spleen, kidneys, and adrenals may also be involved because amyloidosis of the arterial walls occurs both in the secondary form and in paramyloidosis. However, the tremendous amounts of amyloid found in secondary amyloidosis are never pres-ent [illegible]

[illegible] dye after injection is rapidly taken up by the amyloid of the different organs and disappears from the blood serum The more amyloid present in the body, the more dye is removed from the blood stream Thus the Congo-red test is only positive when the deposition of amyloid is very extensive, as in patients in whom nearly the entire liver is replaced by amyloid If the infiltration of the liver is limited, then the Congo-red test cannot be positive, even if kidneys, spleen, and adrenals are involved The amount of amyloid deposited in the latter organs can never be sufficient to absorb so much Congo red that all the dye disappears from the serum It follows that the Congo-red test is only positive in cases of so-called secondary amyloidosis with extensive involvement of the liver, it is often negative in secondary amyloidosis and is never positive in paramyloidosis.

2. Amyloidosis of the kidneys may give rise to severe *proteinuria, hypoproteinemia, edema,* and ultimately *uremia.* This is only observed in cases of so-called secondary amyloidosis, where the kidney in its entirety is involved. If a patient with paramyloidosis develops uremia, then this is never due to the scanty paramyloid infiltration of the blood vessels of the kidney. A patient with paramyloidosis and uremia always suffers from multiple myeloma, and in such cases the uremia is due to the blockage of the tubules by Bence Jones protein, not to the infiltration of the arteriolar walls with amyloid. Significant quantities of Bence Jones protein will always be found in the urine of patients with multiple myeloma and uremia.

3. *Biopsy of the gums* has been advocated for the diagnosis of amyloidosis because amyloid may be present in the arteriolar walls of the submucous layer of the gingiva. This biopsy is only rarely positive in secondary amyloidosis but is certainly important for the diagnosis of paramyloidosis.

4. *Puncture of liver and spleen,* which is often positive in secondary amyloidosis, is of little help in the laboratory diagnosis of paramyloidosis

5. There are several cases on record in which the autopsy of a patient who had suffered from heart failure of unknown origin revealed paramyloidosis of the heart muscle. Only then was the possibility of multiple myeloma considered Examination of the bone marrow in such cases usually proved the existence of generalized myelomatosis.

Since the rarity of tuberculosis, osteomyelitis, syphilis, and leprosy has led to a marked decrease of the cases of secondary amyloidosis, the interest in paramyloidosis has markedly increased

As far as the heart is concerned, cardiac failure does occur, though rarely, in patients with secondary amyloidosis in whom only the arterial system of the heart is involved. Cardiac failure has been observed much more frequently in cases of paramyloidosis, in which the musculature is the prevalent site for it [illegible]

[illegible] myeloma, is usually enlarged

The heart in amyloid disease

Multiple Myeloma and Amyloid Disease

ISADORE SNAPPER

Amyloid Heart Disease

The Heart in Amyloidosis Complicating Multiple Myeloma

ELWYN EVANS

MULTIPLE MYELOMA AND AMYLOID DISEASE

Although *multiple myeloma* is a disease which occurs in all age groups, except during the first decade, it is especially frequent in persons over 40. Therefore, in patients with multiple myeloma and heart failure, the possibility of coronary heart disease must always be considered. Another cause of heart failure in multiple myeloma is associated with the frequent occurrence in this disease of abnormal metabolism of proteins. In this connection Bence Jones proteinuria, hyperglobulinemia, and, especially, amyloidosis must be mentioned. Deposition of amyloid is found in 10 per cent of the patients with multiple myeloma. This form of amyloid degeneration, so-called *paramyloidosis,* frequently involves the myocardium and may lead to intractable myocardial failure

The semantics of this condition are thoroughly confused because the terms "primary" and "secondary" amyloidosis have different meanings for different authors Until 1940, widespread deposition of amyloid, commonly designated as secondary amyloidosis, was often found in the wake of long-standing suppuration and fistulization, especially in cases of tuberculosis, osteomyelitis, syphilis, leprosy, and other chronic diseases With the advent of appropriate antibiotics this form has become relatively rare. Amyloidosis was observed less frequently in patients with chronic rheumatoid arthritis, Hodgkin's disease, and malignant tumors, especially hypernephroma. Occasionally a patient who had not suffered from any of these ailments surprised his physicians when, at autopsy, widespread amyloidosis was discovered. In all these conditions the amyloid deposition was mainly localized in the liver, spleen, kidneys, adrenals, and in the walls of larger and smaller arteries Because the localization of amyloid was always identical, this disorder was commonly designated as *secondary amyloidosis,* even in cases where no clear-cut cause for the degeneration could be found.

Due to deposition in the arterial walls, even in this form, the characteristic substance can be deposited in any organ, including the heart. Arterial amyloidosis usually is not extensive and does not interfere with the function of the involved organ. Exceptions to this rule, however, do occur and severe heart failure has been reported in cases where the so-called secondary amyloidosis had led to widespread involvement of the myocardium.

So-called *primary amyloidosis* or *paramyloidosis* may develop in patients with multiple myeloma. It is mainly localized in striated and smooth musculature, i.e., in the tongue, heart, arterial and arteriolar walls, larynx, esophagus, stomach, and intestines. It also often involves the subcutaneous tissue, lymph nodes, bone marrow, and other parts of the body, e g , the interalveolar septa of the lungs. Primary, or

SUMMARY

In every patient with multiple myeloma and heart failure, the diagnosis of amyloid disease of the heart muscle must be suspected. A rapidly rising pressure and a decreased ventricular systole favor the presence of paramyloidosis The diagnosis is certain if paramyloid is present in subcutaneous tissue or in the subgingival tissue obtained by biopsy.

AMYLOID HEART DISEASE

Cardiac amyloidosis, a rare but distinct type of organic disease in which amyloid deposits occur only or predominantly in the heart, has been receiving increasing attention in recent years Clinical findings are thought to be related to variable deposits of amyloid in the myocardium, pericardium, valves, and the smaller blood vessels.

Although Heubschmann (1907) reported eight cases with amyloid in the heart, and many have been reported since, only four cases of amyloidosis primarily involving the heart were reported by 1930 (Wild; Steinhaus; Beneke and Bonning; Larsen). Cardiac amyloidosis in all probability is a part of systemic amyloid disease and cardiac amyloid involvement is common in primary systemic amyloidosis, as well as in amyloid disease complicating multiple myeloma, and is not rare in secondary amyloidosis, therefore, amyloid disease per se needs to be discussed.

Despite the fact that accurate classification of amyloidosis is impossible because of overlapping of the different types, classification does serve a useful purpose

Lubarsch (1929) distinguished the primary form from the secondary form by (1) the absence of specific causative factors such as tuberculosis, chronic suppurative disease, and rheumatoid arthritis, (2) minimal or no deposition of amyloid in the liver, spleen, kidneys, and adrenal glands, sites of major deposition in the secondary type, (3) maximal deposition in the heart, lungs, skin, digestive tract, and striated muscle, sites not usually involved in the secondary type, (4) tumor formation, and (5) atypical reactions to specific amyloid stains

Reimann et al (1935) proposed the classification most widely used Based on clinicopathological features, they divided amyloidosis into (1) primary, (2) secondary, (3) tumor forming, and (4) that associated with multiple myeloma

ETIOLOGY

It is probable that when the basic cause of amyloidosis is known, all cases will be classified as secondary.

There is no known inciting cause in the primary systemic form which tends to occur in mid-life or later and in an older age group than the secondary form. In 46 cases of primary amyloidosis reviewed by Eisen, ages ranged from 34 to 90 years with an average of 46 years Heredity is a factor in some cases at least. Maxwell and Kimble (1936) were the first to report the familial pattern. Block et al. made extensive genetic studies on 60 members of a family in which there was familial primary systemic amyloidosis; 29 of them had evidence of the disease, and the investigators found it to have a dominant hereditary characteristic.

Age and sex are important factors when amyloid deposits are limited to the heart; these cases usually occur in men over 70 years of age The average age in 29 cases was 82 years (Josselson et al). Although the disorder with amyloid localized in the heart is usually considered a variation of the primary type, the presence of carcinoma in 12 and of multiple myeloma in 1 of the 29 cases is striking Secondary amyloidosis is associated with such inciting diseases as tuberculosis, chronic suppuration, rheumatoid arthritis, carcinoma, Hodgkin's disease and other less commonly associated diseases Amyloidosis associated with multiple myeloma is really secondary to this disease, but is considered separately because its body distribution and staining qualities are similar to those of the primary form.

PATHOGENESIS

Pathogenesis of amyloidosis is unknown There have been numerous theories, but the most favored one is that amyloidosis is related to hyperglobulinemia (Magnus-Levy, 1952, Reimann et al). This relationship has been suggested because of the frequent coexistence of amyloidosis and hyperglobulinemia in cases of multiple myeloma; in horses used for antiserum production, in various animals given repeated injections of bacterial vaccines, and

and its weight is frequently increased to 500 to 600 Gm. Occasionally, at gross examination, a remarkable rigidity and diminished elasticity, together with waxiness of the myocardium, have been found. Both atria and ventricles are often equally involved. Sometimes the cross sections of the myocardium reveal the presence of translucent grayish streaks or patches of amyloid tissue which occasionally completely replace the heart-muscle tissue. Although total obliteration of the arterial lumen by paramyloid rarely occurs, amyloid cushions may project into the lumens of the arteries, especially in the smallest vessels. Due to frequent involvement of the muscular layers of the smaller arteries, ischemic changes of the myocardium with focal areas of necrosis are frequently widespread, while grossly visible necrosis of the heart muscle is rare.

The amyloid deposits may continue from the myocardium into the epicardium and even into the endocardium. The latter are often present in the ventricular aspects of the AV valves near the free margin of the cusps. There may also be uniform thickening of one or more cusps due to subendothelial infiltration of the valve. The mitral and tricuspid valves have been found to be more frequently involved than the aortic or pulmonary valves. Ultimately, the dynamics of such an amyloid valve may be similar to the ones seen in rheumatic heart disease

In the pericardium there may be flattened or round nodules of amyloid deposits

Clinically, amyloidosis of the heart presents an *intractable and progressive heart failure* with or without heart block or other disturbances of the cardiac rhythm Since clear-cut closure of coronary arteries by amyloid is rare, the typical electrocardiogram of myocardial infarction is hardly ever found. Electrocardiography reveals *low voltage* in all leads with *depression of S-T segment, inversion of the T waves, delayed AV conduction,* and irregular rhythm.

The diagnosis of amyloidosis of the heart muscle must be considered in all cases of heart failure of unknown origin which do not react to appropriate therapy. The diagnosis is usually difficult. In this connection, it may be mentioned that the differentiation between paramyloid of the myocardium and rheumatic valvular disease may be impossible, because amyloid of the mitral valve may lead to all the auscultatory signs of a typical mitral valvulitis.

Simultaneous occurrence of heart failure and *polyneuritis* of unknown origin is a strong point in favor of extensive paramyloidosis of the heart muscle.

In every case where the diagnosis of paramyloid disease of the heart muscle is suspected, a *sternal marrow puncture* is mandatory. The greater part of the cases of paramyloid disease of the heart muscle which cause failure are due to multiple myeloma. On the other hand, when, in a patient with heart failure, the bone-marrow puncture proves the presence of multiple myeloma, amyloidosis of the myocardium must be seriously considered.

Gunnar et al. (1956) proved that amyloid infiltration of the heart causes an inability to augment the diastolic volume and underlined the clinical similarities between *amyloidosis* of the heart and constrictive pericarditis. In both conditions, the following signs are encountered:

1. Ascites occurs early, is persistent and, in the later stages, is accompanied by peripheral edema

2. Venous pressure is high, pulse pressure is low.

3 A paradoxical pulse may be present

4. The electrocardiographic changes are nonspecific.

5. There is little or no response to conventional treatment of cardiac failure.

Thus, it can be understood that, in certain cases of myocardial amyloidosis, surgical procedures have been erroneously performed

As emphasized by Gunnar et al , catheterization reveals in both diseases that the diastolic filling of the ventricles is markedly impaired. This is due in constrictive pericarditis to the incarceration of the ventricle by scar tissue, this leads to the loss of the elasticity of the epicardium and the superficial myocardial muscle layers. In amyloidosis of the heart, the abnormal protein, amassed between the muscle fibers, interferes with the diastolic expansion of the ventricles. Catheterization of the right ventricle registers an early diastolic dip, then a sudden rise, and high end-diastolic pressure. The right atrial pressure is, of course, abnormally high.

Cardiac output is diminished and systolic pressure is much lower than expected in the presence of a high diastolic pre[illegible]re.

25 each, extremity pain in 19, enlarged lymph nodes in 18, abdominal pain in 10, hematuria in 5, hematemesis in 4, fever in 3, and purpura in 1.

Myocardial failure was sufficiently severe to be considered the cause of death in 25 of 46 cases (Dahlin, 1949a).

In the cases in which amyloid deposition is confined to the heart, the signs and symptoms are those of congestive failure in patients about 70 years of age or older, usually males In 15 of these patients, atrial fibrillation was found on seven occasions (Josselson and Pruitt)

Occasionally, *chronic constrictive pericarditis is simulated* (Findley and Adams; Gunnar et al). In both conditions, there is a loss of distensibility and resistance to contraction, and clinically there may be narrow pulse pressures, feeble cardiac pulsations, high venous pressures, evidence of myocardial failure unresponsive to usual forms of therapy, and nonspecific electrocardiographic changes.

When organs other than the heart are involved, signs and symptoms related to these structures naturally appear. In macroglossia, the tongue is usually hard and nontender, and is often associated with dysphagia and dysarthria. When the trachea, mediastinum, or the vessels of the lungs are involved, dyspnea may be associated with a picture of chronic cor pulmonale

Contrary to the general belief, involvement of the liver and spleen is not uncommon in the primary systemic form When it is sufficiently infiltrated, it may be palpably enlarged, hard, and not tender unless the enlargement is partly due to congestive heart failure. Liver function may or may not be impaired, but clinical evidence of serious impairment of liver function is not common Ascites was present in 29 per cent of 71 cases reported by Higgins and Higgins Jaundice is uncommon, but was present in 7 of 50 cases reviewed by Mathews When the spleen is involved, it may be palpably enlarged, but usually not greatly. The gastrointestinal tract was involved in 33 of 54 patients, five of whom had serious hemorrhages (Dahlin, 1949) The gastrointestinal symptoms and signs have been diarrhea, constipation, abdominal pain, nausea, vomiting, distention, intestinal hemorrhage ...

About one-third of the patients with systemic amyloidosis tend to develop the nephrotic syndrome which varies in severity from albuminuria with edema to the full-blown picture of nephrosis (Pruitt et al.). Occasionally, there is sufficient amyloid involvement of the glomeruli to cause azotemia.

Lindsay found skin lesions described as opalescent and papular, or opalescent, firm, nodular, sclerodermic, and papular, with plaquelike scleroderma, weeping eczema, and pink striae beneath the nails of the fingers and toes. Mathews mentioned purpura or petechiae in 9 of the 50 cases he reviewed Occasionally, muscular, joint, or tendon involvement is associated with some joint distress or ... ment m... like, bu... say).

Secondary Amyloidosis. Signs and symptoms of organ involvement in the secondary form occurs most often in cases with renal infiltration, especially when the nephrotic syndrome is present. Dahlin (1949) observed albumin in 26 of 27 cases, but renal failure was severe in only three Muscle involvement and macroglossia are absent. Although the heart is involved in only about 10 per cent of cases of the secondary type, signs and symptoms are similar to those of the primary type with enlargement and progressive, unresponsive congestive failure. Hepatomegaly with an enlarged, hard, and nontender liver is the main evidence of liver involvement, occurring in two-thirds of 102 cases, but disturbance of liver function is only evident occasionally. Jaundice has been noted only three times in the literature. Splenomegaly, usually slight to moderate, may be noted. In spite of the fact that most authors emphasize frequent involvement of the adrenal glands pathologically, especially in the secondary type, impairment of adrenal function is rarely mentioned in either type. Although clinical evidence of Addison's disease is not frequent in amyloidosis, amyloid involvement of the adrenals was the third most common cause of Addison's disease in O'Donnell's series In 29 cases of moderately advanced adrenal amyloidosis, evidence of hypoadrenocortical function was present in only three

LABORATORY STUDIES

CONGO-RED TEST The Congo-red test is the only laboratory procedure of real diagnostic value other than biopsy of pathologic material ... this test ... of sufficient amyloid de-

in rabbits fed or injected with sodium caseinate.

Even the site of formation of amyloid is disputed. The two main views are: (1) Amyloid is deposited primarily in or on the cell membrane (Peters, 1943). (2) It is deposited beneath the capillary endothelium, whence it spreads (Larsen). Magnus-Levy (1952) thinks that amyloid is formed in the plasma cell and that Herbut and Erf and Bayrd and Bennett proved this theory when they found amyloid within the myeloma plasma cell, since this cell is not phagocytic.

PATHOLOGICAL CHANGES

Reviewing 70 cases of primary amyloidosis, Dahlin (1949a) noted a marked tendency to involve the heart, lungs, muscles (smooth and striated), skin, and other structures of mesodermal origin not often involved, at least to a serious degree, in secondary amyloidosis. Eisen, reviewing 46 primary cases with autopsy studies found the myocardium to be involved in 85 per cent, endocardium, in 61 per cent, pericardium, in 48 per cent, valves, in 37 per cent, stomach, in 57 per cent, small intestine, in 52 per cent, colon and tongue, each in 48 per cent, skin and spleen, each in 27 per cent; kidneys, in 26 per cent, and liver and lymph nodes, each in 17 per cent.

The bulk of cardiac amyloid is myocardial in distribution, the myocardium being firm and resistant to cutting. All chambers may be involved, and may be hypertrophied, thickened, stiff, and leathery. When amyloid is grossly visible in the heart, it appears patchy or diffuse, translucent, waxy, and grey, pinkish, or yellowish. Macroscopically, it becomes brownish with the application of iodine and turns darker with the addition of dilute sulfuric acid.

Microscopically, amyloid is diffusely deposited throughout the interstitial tissue, and muscle fibers become atrophic, fragmented, vacuolated, or necrotic. Amyloid is found in the veins, capillaries, arterioles, and sometimes in any or all layers of the larger coronary arteries (Mathews).

In elderly individuals, 70 years of age or more, deposits may be confined to the heart, these are usually small and confined in distribution, but occasionally are large. Josselson et al. (1952), studying 29 cases of amyloid disease localized in the heart, found atrial endocardial deposits to be grossly recognizable in 22 of them. The atrial endocardial deposits appeared as tiny, translucent, grey, or pink elevations either in localized collections or deposited diffusely. While the atrial endocardium showed quite striking changes, the ventricular endocardium usually showed little or no change. In 3 of 13 cases reported as amyloidosis localized in the heart, small amounts of amyloid also were found in the lung or prostate gland (Josselson et al, 1950).

In the primary form, the amyloid, to variable degrees, stains red with Congo red, periodic acid, and leucofuchsin; metachromatically reddish-violet with methyl or crystal violet and methyl green; brownish with iodine; and yellow or pale pink with van Gieson's stain

The secondary type predominantly involves the liver, spleen, kidneys, and adrenal glands Occasionally the heart is involved, rarely extensively. Dahlin (1949b) found the spleen to be involved in 100 per cent; kidneys, in 93 per cent; liver, in 87 per cent; lymph nodes, in 68 per cent; gastrointestinal tract, in 55 per cent; heart, in 10 per cent; and striated muscle 0 per cent. The liver was *not often* infiltrated extensively.

The amyloid found in secondary amyloidosis stains consistently and typically with the various amyloid stains

CLINICAL DESCRIPTION

Signs and symptoms are extremely variable in number and severity because of variations in the number of organs involved and the extent of the involvement.

Primary Amyloidosis. Despite the variability of signs and symptoms in the primary form, a fairly definite clinical pattern is not uncommonly revealed with persistent, unresponsive myocardial failure of unknown origin associated with macroglossia in 42 per cent, asthenia in 42 per cent, and weight loss in 31 per cent. This pattern is not likely to be seen in any other condition and differentiates the primary form clinically from the secondary form In a series of 71 cases of primary systemic amyloidosis reviewed by Higgins and Higgins, *congestive failure* was present in 40 patients (56 per cent), *dyspnea and edema* were present in 39 per cent of these patients, *ascites* in 19 per cent, and *hydrothorax* in 18 per cent Macroglossia was present in 25 patients, 18 of them had dysarthria and 15, dysphagia General muscular weakness was present in 36 patients, skin and buccal membrane deposits in

wave abnormalities in twelve. Serial changes were noted in four cases in which more than one electrocardiogram was taken.

Josselson et al. (1953) studied the electrocardiograms of 15 patients found to have amyloid in their hearts at autopsy. Four were primary systemic, ten amyloidosis localized in the heart, and one cardiac amyloidosis associated with multiple myeloma. The tracings were abnormal in twelve cases. The most common abnormality was low voltage of the QRS complexes in the standard limb leads. It was interesting that *atrial fibrillation* was present in seven patients. This was thought to be abnormally high because electrocardiograms had been taken on the basis of suspected cardiac disease, and atrial fibrillation is an indication for obtaining an electrocardiogram. There were two cases with *complete* AV block, but there were no prolonged P-R intervals otherwise, and none of the electrocardiograms justified the diagnosis of myocardial infarction. *Low voltage* of the QRS complexes in leads V_1, V_2, and V_3, with normal complexes between and in the transitional zone was commented upon. Mild atherosclerosis was common, but not sufficient to be clinically significant.

Although the electrocardiographic findings are not specific for cardiac amyloidosis, low voltage of the QRS complexes in the standard limb leads and low, isoelectric or diphasic T waves with or without impairment of AV conduction or atrial fibrillation *are not especially* common in other diseases, and when considered with the clinical pattern and other laboratory tests, the electrocardiogram may be suggestive.

URINALYSIS. The kidneys were involved in 93 per cent of the secondary cases, and about one-third of the patients with the primary form developed the nephrotic syndrome (Dahlin, 1950). Renal involvement is *usually manifested* (1) by albuminuria of various degrees, *occasionally* massive, (2) occasionally by fixed specific gravity and (3) by findings associated with azotemia.

BLOOD COUNT. The blood count *frequently* revealed a hypochromic normocytic anemia of variable degree, but nothing otherwise significant. The sedimentation rate *is frequently increased* in the primary type, often *slightly to moderately*. In the secondary form, the blood *count often* shows secondary anemia and some leucocytosis. The sedimentation rate *is* often elevated.

LIVER FUNCTION STUDIES. Although the liver is almost universally involved in the secondary form and in about 30 to 40 per cent of the patients with the primary form, it often is not infiltrated sufficiently to show liver dysfunction. Severe liver disturbance is only occasionally noted, although it is not uncommon to observe some Bromsulphalein retention, together with elevation of alkaline phosphatase and serum cholesterol, hypoalbuminemia, and normal serum bilirubin. Abnormal cephalin flocculation and thymol turbidity tests are rare. The picture often simulates biliary obstruction without elevation of serum bilirubin.

CATHETERIZATION STUDIES. Catheterization studies in cases simulating chronic constrictive pericarditis yielded results indistinguishable from those of constrictive *pericarditis* (Gunnar et al; see also Chap. 12, Cardiac Catheterization in Subendocardial Fibroelastosis and Constrictive Diseases).

SERUM ELECTROPHORETIC STUDIES. Block *et al.* studied serum electrophoretic *findings in* 60 members *of a family* in which there was familial primary systemic amyloidosis. Twenty-nine patients showed an atypical protein peak in the $alpha_2$ and beta globulins, 14 of them showed poor resolution *in the* $alpha_2$ *globulin region*. All patients with clinical manifestations of the disease had *atypical* electrophoretic patterns, *but* 18 of the patients with abnormal electrophoretic patterns had no clinical manifestations.

LIPOPROTEIN STUDIES. Rukavina et al. made serum lipoprotein studies on 33 members of the family mentioned above, and found elevations of *the* $-S$ *fractions in* 27 of them. There appeared *to be a correlation between* the lipotrophic changes *and clinical* manifestations.

DIAGNOSIS

Diagnosis of amyloidosis limited to the heart is practically impossible, but may be suspected when intractable congestive heart failure of unknown origin appears in elderly persons about the age of 70 years or beyond, especially men.

Although electrocardiographic abnormalities are common at this age and electrocardiographic changes in cardiac amyloidosis are nonspecific, low voltage of the QRS complexes in the standard limb leads associated with T-wave abnormalities with or without atrial fibrillation or impaired AV conduction, should be suggestive, especially when associated with the clinical picture described above.

posits in the body and the frequent lack of affinity for the dye by the amyloid that is present. It is positive in less than half of the primary cases and is usually equivocal. Another objection to the use of intravenous Congo red is that it is not entirely safe. It should be used with caution in elderly individuals and in patients who have previously received the dye. Selikoff and Bernstein reported six serious systemic reactions, with two fatalities, in 100 consecutive cases in which the intravenous dye was used. All patients with severe reactions had received the dye previously without reaction It also should be used with caution when the skin is involved, and perhaps should not be used at all when skin involvement is extensive or in exposed surfaces because of the possibility of stubborn, fiery-red staining of the tissues.

Bennhold considered 60 per cent removal of the dye from the serum between 4-min and 60-min samples presumptive evidence of systemic amyloidosis. Because false-positive results occasionally appear, several investigators have modified Bennhold's technique, but none of the modifications have eliminated the basic criticism that variable amounts of the dye are absorbed by nonamyloid tissues, thereby making impossible the diagnosis of amyloid in the tissue in minimal or early cases To eliminate false-positive results, the criterion of 90 to 100 per cent removal of the dye in the 1-hr sample has been suggested Unger et al removed specimens at 2- or 4-min and 30-min intervals, and considered removal of 35 per cent of the dye between the 2- or 4-min and 30-min specimens as presumptive evidence of amyloidosis.

The intravenous Congo-red test is of more value in the secondary type of amyloidosis because of more frequent and often more extensive liver involvement. The test also is likely to be more positive in secondary amyloidosis because of the much greater affinity of the amyloid tissue for the dye in this type of the disorder.

Local injections of Congo red may be used when mucous membrane or skin lesions are present. It is a useful test, but tissues may not take the dye up readily in primary cases Here too, it must be remembered that skin discoloration may persist

TISSUE BIOPSY. Biopsy of the involved tissue is the only certain diagnostic measure It is also of special value in those cases with skin involvement because it avoids the danger of persistent staining. Biopsy occasionally may be falsely negative because the particular section taken does not happen to contain amyloid material and, in the primary systemic type, because of lack of affinity of the amyloid tissue for the various amyloid stains Biopsy of the tongue, mucous membranes, striated muscles, skin, tendons, liver, and even the stomach have yielded positive and diagnostic results in primary systemic amyloidosis. Biopsy of the liver and spleen in the secondary type have occasionally been diagnostic. Needle biopsies of the liver were positive in seven cases thought to have primary systemic amyloidosis (Pruitt et al, 1953). Unfortunately, differences between the primary and secondary forms are not always clear-cut, and Pruitt et al mentioned this. Because of one reported case of fatal hemorrhage from the liver following liver biopsy, Pruitt et al advise that, if congestive failure is evident, appropriate treatment should be carried out for several days before the liver biopsy in order to reduce the venous pressure as much as possible.

Selikoff and Robitzek performed gingival biopsies on 47 patients with secondary amyloidosis without gross evidence of gingival involvement. Biopsies were positive in 14 of 18 patients in whom the diagnosis of amyloidosis could be made with reasonable certainty. These authors recommended biopsy of gingival tissues because of their accessibility, the simplicity of the technique, the resistance of the tissues to infection, and the freedom from danger of severe hemorrhage.

Because cardiac amyloidosis may occasionally simulate chronic constrictive pericarditis (Maxwell and Kimble, Gunnar et al.) and pericardiectomy might be contemplated, Josselson et al. (1952) suggested *myocardial biopsies* in these cases before pericardiectomy is done. Sections of the left atrial appendage were studied in 11 of their 29 cases of amyloidosis localized in the heart, and amyloid was found in 7 of the 11 cases.

ELECTROCARDIOGRAM The electrocardiogram is usually abnormal when amyloid deposits are present in the heart, but changes are non-specific, although the particular findings may be suggestive when considered with the rest of the picture. Wessler and Freedburg presented two cases, and analyzed the electrocardiograms in nineteen published cases in which the electrocardiograms were recorded. Their two cases showed definite Q waves in the precordial leads suggestive of anterior myocardial infarction. An autopsy on one of these patients showed amyloid deposits but no infarct, fibrosis, or narrowing of the coronary vessels. No uniform pattern was elicited, but all electrocardiograms were abnormal There was prolongation of the P-R interval in six patients, low voltage of the QRS complexes in the standard limb leads in twelve, deep Q waves in the precordial leads in two, and P-

wave abnormalities in twelve. Serial changes were noted in four cases in which more than one electrocardiogram was taken.

Josselson et al. (1953) studied the electrocardiograms of 15 patients found to have amyloid in their hearts at autopsy: four were primary systemic; ten amyloidosis localized in the heart, and one cardiac amyloidosis associated with multiple myeloma. The tracings were abnormal in twelve cases. The most common abnormality was low voltage of the QRS complexes in the standard limb leads. It was interesting that *atrial fibrillation* was present in seven patients. This was thought to be abnormally high because electrocardiograms had been taken on the basis of suspected cardiac disease, and atrial fibrillation is an indication for obtaining an electrocardiogram. There were two cases with *complete AV block*, but there were no prolonged P-R intervals otherwise, and none of the electrocardiograms justified the diagnosis of myocardial infarction. *Low voltage* of the QRS complexes in leads V_1, V_5, and V_6, with normal complexes between and in the transitional zone was commented upon. Mild atherosclerosis was common, but not sufficient to be clinically significant.

Although the electrocardiographic findings are not specific for cardiac amyloidosis, low voltage of the QRS complexes in the standard limb leads and low, isoelectric or diphasic T waves with or without impairment of AV conduction or atrial fibrillation are not especially common in other diseases, and when considered with the clinical pattern and other laboratory tests, the electrocardiogram may be suggestive.

URINALYSIS. The kidneys were involved in 93 per cent of the secondary cases, and about one-third of the patients with the primary form developed the nephrotic syndrome (Dahlin, 1950). Renal involvement is usually manifested (1) by albuminuria of various degrees, occasionally massive, (2) occasionally by fixed specific gravity and (3) by findings associated with azotemia.

BLOOD COUNT. The blood count frequently revealed a hypochromic normocytic anemia of variable degree, but nothing otherwise significant. The sedimentation rate is frequently increased in the primary type, often slightly to moderately. In the secondary form, the blood count often shows secondary anemia and some leucocytosis. The sedimentation rate is often elevated.

LIVER FUNCTION STUDIES. Although the liver is almost universally involved in the secondary form and in about 30 to 40 per cent of the patients with the primary form, it often is not infiltrated sufficiently to show liver dysfunction. Severe liver disturbance is only occasionally noted, although it is not uncommon to observe some Bromsulphalein retention, together with elevation of alkaline phosphatase and serum cholesterol, hypoalbuminemia, and normal serum bilirubin. Abnormal cephalin flocculation and thymol turbidity tests are rare. The picture often simulates biliary obstruction without elevation of serum bilirubin.

CATHETERIZATION STUDIES. Catheterization studies in cases simulating chronic constrictive pericarditis yielded results indistinguishable from those of constrictive pericarditis (Gunnar et al.; see also Chap. 12, Cardiac Catheterization in Subendocardial Fibroelastosis and Constrictive Diseases).

SERUM ELECTROPHORETIC STUDIES. Block et al. studied serum electrophoretic findings in 66 members of a family in which there was familial primary systemic amyloidosis. Twenty-nine patients showed an atypical protein peak in the $alpha_2$ and beta globulins, 14 of them showed poor resolution in the $alpha_2$ globulin region. All patients with clinical manifestations of the disease had atypical electrophoretic patterns, but 16 of the patients with abnormal electrophoretic patterns had no clinical manifestations.

LIPOPROTEIN STUDIES. Rukavina et al. made serum lipoprotein studies on 33 members of the family mentioned above, and found elevations of the $-S$ fractions in 27 of them. There appeared to be a correlation between the lipotrophic changes and clinical manifestations.

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low temperatures, showed any significant effect in preventing development of amyloidosis in albino mice. The author suspects that liver is not helpful in most cases, because others have reported failures with its use and most authors have not mentioned its use in their own cases, although many have referred to Grayzel's favorable results

THE HEART IN AMYLOIDOSIS COMPLICATING MULTIPLE MYELO

The heart is not involved in multiple myeloma unless this disease is complicated by amyloidosis, this apparently occurs in about 15 per cent of the cases (Bayrd and Bennett). Magnus-Levy (1933) reported 35 instances in 150 cases, and Snapper et al. reported 8 instances in 41 autopsied cases

Justifiably all authors on the subject of amyloidosis have classified amyloidosis in multiple myeloma separately. Although amyloidosis is secondary to multiple myeloma, it has the characteristics of primary systemic amyloidosis

ETIOLOGY AND PATHOGENESIS

The basic cause of both diseases is unknown. The most favored theory for the pathogenesis of amyloidosis is that it is related to hyperglobulinemia (Magnus-Levy; Reimann et al) because of their coexistence in experimental animals and in many diseases, especially multiple myeloma Magnus-Levy (1952) thinks that amyloidosis and multiple myeloma are disturbances of protein metabolism and originate in the plasma cell

PATHOLOGICAL PICTURE

The pathological picture of amyloidosis, especially in relationship to the heart and blood vessels, is discussed in detail earlier in this chapter.

Amyloidosis secondary to multiple myeloma has the atypical anatomic distribution and the atypical staining reactions of primary systemic amyloidosis Occasionally, amyloid will form intraosseous tumors, at times obscuring the underlying plasmocytoma within which it arises The digestive tract was involved in seven and the heart in five of eight autopsied cases of amyloidosis complicating multiple myeloma (Snapper et al.)

The bones most commonly involved in multiple myeloma are cancellous bones with considerable red bone marrow, especially flat bones such as the ribs, sternum, clavicle, skull, and pelvis, and the vertebrae and proximal ends of the femur and humerus Classically, ..crete lesions occur in the flat bones, but diffuse demineralization is more common. Pathological fractures, especially compression fractures of the vertebrae, are common. Geschicter and Copeland found nephritis in 86 per cent of the kidneys examined.

Of 30 consecutive autopsies at Mount Sinai Hospital, 73 per cent were found to have diffuse or nodular infiltration of the liver, spleen, and lymph nodes with myeloma cells.

CLINICAL DESCRIPTION

Patients with multiple myeloma usually seek medical advice because of skeletal symptoms Major complaints in order of frequency, alone or in combination, are pain, especially of back and thorax, weight loss, pathological fractures, and palpable tumors of superficial flat bones (Lichtenstein and Jaffe).

The onset is often insidious, but occasionally the onset is sudden, especially with bone fracture or collapse of a vertebra. Oddly, in amyloidosis complicating multiple myeloma, the incidence of bone pains and of bone lesions seen on roentgenography becomes less frequent Five of eleven patients with amyloidosis had no roentgenographic evidence of bone involvement and only one of these had significant bone pain (Snapper et al.). Signs and symptoms of neuritis appeared in 40 per cent. Bleeding tendencies were mentioned by several authors Snapper et al. noted hemorrhagic tendencies in 35 per cent. Renal involvement is common and occasionally severe Geschicter and Copeland found 61 per cent to have Bence Jones proteinuria In the series studied by Snapper et al , 13 of 41 cases autopsied showed microscopic pathology of myeloid kidney; nine of these died in severe uremia. The blood pressure is usually normal, even in the presence of uremia, a phenomenon which helps confirm the impression that the myelomatous kidney is nonhypertensive. Of 97 patients, palpable hepatomegaly was present in 40 per cent and hepatosplenomegaly was present in 23 per cent. The liver was smooth, firm, and usually nontender. The lymph glands were less frequently enlarged, and usually only moderately

Primary Systemic Amyloidosis. When similar cardiac findings are associated with signs or symptoms of involvement of other organs, *diagnosis is* possible and *amyloidosis* often should be suspected. When other organs are involved, other causes for their involvement naturally should be considered. Macroglossia, which occurs in 40 per cent of amyloidosis cases, is important because it is uncommon otherwise. Cirrhosis of the liver should be considered when ascites occurs, especially when associated with jaundice. The general opinion is that the liver and spleen are not commonly involved; however, Higgins and Higgins found clinical involvement in these organs in 60 per cent of 23 cases. When the liver is enlarged due to amyloid deposits and not congestive failure, *it is hard and not tender.* When liver function is disturbed, liver function tests are usually more abnormal than one would expect *from congestive failure alone, suggesting* primary hepatic disease. Jaundice may occur and attract attention to liver disease, especially in the primary form, in which it has been reported six times (Dahlin, 1949) Needle biopsy of the liver may be negative in the presence of amyloidosis with hepatomegaly, but is likely to be positive Renal involvement with the nephrotic picture occurs in about one-third of the cases When the nephrotic picture is associated with myocardial failure, the edema may be greater than might be expected from the nephrosis alone, and the albuminuria is often greater than one would expect from congestive failure alone Occasionally azotemia reveals the existence of organic renal disease

Digestive tract symptoms may be vague or bizarre, and, without evidence of involvement elsewhere in the body, diagnosis of amyloidosis is difficult The digestive tract was involved in 25 of 54 cases reported by Dahlin (1950). Many of these patients had no symptoms referable to the digestive tract, but five had serious hemorrhage and three simulated carcinoma of the stomach Gastric ulcers were reported in three cases (Lindsay) Rarely, there is clinical evidence of intestinal obstruction due to infiltration of the intestinal wall without obliteration of the intestinal lumen Adrenal hypofunction may be suspected because of muscular weakness, but other findings consistent with adrenal hypofunction are rare, especially in the primary type. *Myasthenia gravis is readily ruled out.* Joint involvement with limitation of motion and occasional pain in extremities may simulate arthritis. Muscle or tendon biopsy may confirm the diagnosis. Various skin diseases may be suspected, and with ecchymoses, petechiae, and scleroderma-like lesions, one should suspect some systemic disease.

In cases simulating chronic constrictive pericarditis, careful search for evidence of other organ involvement may be fruitful The clinical pattern of intractable heart failure with macroglossia (present in 40 per cent of the cases), general muscular weakness (50 per cent), and weight loss (40 per cent), with or without other clinical evidence should give one a clue as to the diagnosis as well as *differentiate the primary* from the secondary form. Other clinical combinations also should be suggestive and any additional clinical evi*dence should make the* diagnosis relatively easy if one just thinks of the disease

In the *secondary form,* the heart is involved *in about 10 per cent of the* cases Nonresponsive heart failure, developing in a patient with one of the common inciting diseases, should arouse suspicion of *amyloidosis,* with or without evidence of further organ involvement.

With renal involvement, *albuminuria* is usually greater than with congestive failure alone.

PROGNOSIS

Primary amyloidosis is 100 per cent fatal In Eisen's series, the average duration of the disease after the onset of symptoms was 32 months; the longest duration was 14 years After the onset of symptoms in the secondary form, 82 per cent succumbed within 1 year (Eisen); however, a few cases have been known to recover after removal of the inciting cause.

TREATMENT

Treatment of primary amyloidosis is *purely* symptomatic and directed at complications

Treatment of secondary amyloidosis is primarily directed at removal of the *inciting disease,* however, powdered whole liver may be helpful Grayzel et al. (1938) reported relief with the use of 4 to 8 Gm of powdered whole liver daily. After using 14 different preparations, Grayzel et al. (1956) found that only powdered whole liver, desiccated at relatively

ated by electrophoretic separation or Howe fractionation.

In metastatic carcinoma, bone lesions are usually not so clear-cut and often show osteoblastic changes, and the serum alkaline phosphatase is often elevated. Skeletal demineralization in senile osteoporosis is usually limited to the spine and pelvis In hyperparathyroidism, serum calcium and alkaline phosphatase are increased and the serum phosphorus is decreased.

PROGNOSIS

Multiple myeloma is 100 per cent fatal, and the downhill progress may be hastened if amyloidosis appears, especially if it involves the heart. When Bayrd and Bennett reported their series of 66 patients, 55 had died. The shortest survival period after the onset of symptoms was 1 month and the longest 24 months, with an average of almost 19 months.

TREATMENT

Treatment is primarily symptomatic. Radiotherapy gives some palliative relief, especially when pressure symptoms occur, and administration of stilbamide, urethane, ACTH and cortisone may be followed by periods of wellbeing, but the general course of the disease remains unchanged.

so. Weakness is common, and emaciation is frequent in advanced stages.

Five of eight autopsied cases with amyloidosis complicating multiple myeloma revealed *cardiac involvement*, and four of these died of congestive failure (Snapper et al.). Four of the eight cases died in uremia; of these three had myelomatous kidneys and the fourth had a combination of myelomatous kidneys and amyloidosis. Only one of the eight patients had hypertension, and he did not die of uremia. Ten per cent of the patients with amyloidosis in multiple myeloma have macroglossia (Bayrd and Bennett).

LABORATORY STUDIES

Roentgenographic Examination. Two types of bone lesions are recognizable on roentgenograms in multiple myeloma: (1) typical, multiple, discrete, lytic lesions without bone production, especially in the flat bones, and (2) diffuse demineralization, especially in the vertebrae. Bone lesions may be absent, and this is especially true if amyloidosis is present.

Urinalysis. Bence Jones proteinuria, a most significant finding, is present in about 50 per cent of the cases, but may be present at one time and not at another. A 24-hr specimen will sometimes be positive when isolated specimens are negative.

Blood Studies. Snapper et al found in 97 consecutive cases of multiple myeloma that the *total serum protein level* was above 8 Gm/100 ml in 72 per cent of the cases In 45 per cent of these, the serum globulin exceeded 7 Gm/100 ml. *Albuminemia* was found in all cases studied

In *blood serum* studies, calcium is often elevated, inorganic phosphorus is usually normal, except in the presence of uremia when it is high, alkaline phosphatase is usually normal, except in the presence of fractures when it may be elevated, and uric acid is commonly elevated. Serum uric acid was above 4 mg/100 ml in 87 per cent of the patients (Snapper et al).

Electrophoretic studies are helpful in differentiating the various protein fractions of the serum. Gamma globulin predominates in multiple myeloma.

In multiple myeloma, *peripheral blood studies* reveal moderate to severe normocytic, hypochromic anemia as one of the most common findings The leucocyte count is variable. Plasma cells are usually elevated, and should be looked for carefully. Excessive rouleaux formation occurs in over half of the patients.

A rapid erythrocyte *sedimentation rate* is characteristic; however, 10 of 97 consecutive patients had normal sedimentation rates, and none of them had elevated serum globulin levels (Snapper et al.).

DIAGNOSIS

Diagnosis of amyloidosis in multiple myeloma is intriguing. The first essential is to think of these diseases, especially in bizarre cases Amyloidosis should be looked for carefully in all cases of multiple myeloma, and vice versa. Amyloidosis occurs in about 10 per cent of the patients with multiple myeloma, and the latter is not an uncommon cause of the picture of primary systemic amyloidosis. Amyloidosis should be suspected in all cases of multiple myeloma in which there is congestive heart failure or macroglossia, neither of which occur in uncomplicated multiple myeloma. With amyloid involvement of several muscles, tendons, and joints, rheumatoid arthritis may be suspected.

Clinically, pain, especially back or rib pain, weakness, tumors of superficial flat bones, hyperproteinemia, especially hyperglobulinemia, and punched-out osteolytic bone lesions or compression of vertebrae, alone, but especially in combination, should cause one to check further for multiple myeloma However, it should be remembered that bone pains and bone lesions seen on roentgenography are much less frequent when amyloidosis complicates multiple myeloma

Hypercalcemia, an elevated serum uric acid, uremia without hypertension, albuminuria, hepatosplenomegaly, and unexplained anemia, fever, or hemorrhagic tendencies should also cause one to consider multiple myeloma. If Bence Jones proteinuria, which occurs in 50 per cent of the cases, is present, multiple myeloma is almost certain. Myeloma cells in bone-marrow biopsies, of course, are diagnostic Fortunately, most patients will have Bence Jones proteinuria or hyperglobulinemia; however, hyperglobulinemia is less pathognomonic, because it occurs in other diseases such as acute lupus erythematosis, cirrhosis of the liver, kala-azar and other diseases If necessary, the globulins in these diseases can usually be differenti-

is the primary site of the malignancy. A similar behavior is shown by primary pericardial sarcoma and myxofibrosarcoma.

Myocardium. Rhabdomyoma and sarcoma are the two most common myocardial tumors. In contrast to sarcoma, which is mostly seen in aged persons, well over one-half of the rhabdomyomas occur in individuals under 1 year of age.

The term *rhabdomyoma* is a misnomer firmly fixed in the literature. Sussman and Stasney have termed the process "congenital glycogenic tumor of the heart." Since it has been convincingly proved that the condition results from a separation or a focal arrest in maturation of striated muscle during embryonic development, this term fits well into the concept of a dysontogenetic process.

Of the 69 cases analyzed by Kidder, over 50 per cent were associated with other anomalies (harelip, cleft palate, sebaceous gland adenomas, cysts and tumors of the kidneys, and so on), the most common being tuberous *sclerosis.* Steinbiss has explained the frequent association of rhabdomyomas with tuberous sclerosis on the assumption of an excess of glycogen in the brain and heart *blastemas.*

Fifty-two per cent of the patients with cardiac rhabdomyoma die in the first year of life and 86 per cent before they reach puberty. The youngest patient on record was a 6-month fetus, the oldest, a 45-year-old man. Males and females are almost equally affected, with a slight predominance in the male (60 per cent). The absence of any appreciable racial predilection is indicated by observations in Negroes and Japanese. Any portion of the heart may be involved by the condition, including the valve leaflets, in the majority of cases several noncapsulated, soft, discrete, yellowish-white nodules are found. A single, coarsely fasciculated nodule, grossly resembling a fibroma, was present in one case.

The most prominent histological characteristic of the nodule is the so-called "spider cell," characterized by a large nucleus suspended by threads of cytoplasm between large vacuoles. Von Recklinghausen, in the first case report, considered the vacuoles to be dilated lymph spaces. Virchow also conceived that the content of the vacuoles was either lymph or serous fluid. The glycogenic component of the "spider cell" was suggested by Seiffert and proved by Wolbach. Since the myofibril passes through a "spider-cell phase" during development, it is quite obvious that the rhabdomyomatous nodule represents a focal arrest in the maturation of cardiac muscle fibers. Along this line, a possible relationship between cardiac rhabdomyoma, "congenital" hypertrophy of the heart, and von Gierke's disease has been suggested.

As commonly applied, the term *hamartoma* designates a tumor resulting from arrested development of elements normally present in the organ where the tumor is found. In addition to myofibrils, fibrous tissue, blood vessels, nerves, and fat enter in the composition of the heart. Any of these tissues can be the potential source of developmental error or tumor growth in a true sense. Since the two conditions are often difficult to differentiate, they may be conveniently considered together. Fibroelastic, fibrolipomatous, fibromatous, and lipomatous growths have been described. Intramyocardial hemangiomas and lymphangiomas have also been recorded. "Epithelial inclusion cysts" have been variously interpreted as arising from sequestration of cells of the foregut or from metaplasia of mesodermal elements.

Primary malignant tumors of the myocardium are less common than benign tumors, the ratio being estimated as about 1:16. Myofibrils have little, if any, regenerative power, and this fact explains the extreme rarity of primary malignant muscle tumors. Nine such cases have been reported in the literature, characterized mainly by the straplike shape of the cells, strongly acidophilic cytoplasm, formation of syncytial strands, and sporadically by the presence of large vacuolated giant cells and by striations within the neoplastic cells.

The sarcoma group of more frequent occurrence runs the gamut of mesenchymal tumors: fibrosarcomas, fibromyxosarcomas, myxosarcomas, lymphosarcomas, reticulum-cell sarcomas, leiomyosarcomas, round-, spindle-, and mixed-cell sarcomas; 143 of these had been described up to 1955. *Kaposi's disease* of the heart has also been recorded. The great variety of diagnostic terms used by the individual authors reflects the uncertainty of the criteria that are to be met in any attempt at classifying the connective tissue growths in general.

The symptom complex of myocardial sar-

Neoplasms of the heart

Pathological Aspects

C. GEORGE TEDESCHI

Clinical Aspects

FRANKLIN C. MASSEY

PATHOLOGICAL ASPECTS

Boneti (1679) and Morgagni (1761) have both been credited with descriptions of primary tumors of the heart. In the following two centuries, several hundred cases have been slowly accumulated and, in a review of the world literature, Mahaim gathered 413 primary growths of the heart and pericardium

Although it is generally agreed that primary tumors of the heart occur rarely, data on their actual frequency vary considerably Assuming all cases to have been reported, incidence ranges from 0 33 per cent, in the Pollia and Gogol review of 46,072 autopsies, to 0 0017 per cent in the National Survey of 480,331 autopsies between 1938 and 1942.

New interest is being injected into this subject by sporadic reports of cases in which the condition was diagnosed during life and successfully corrected by means of surgery. Since at least some of the cardiac tumors are amenable to surgical treatment, their recognition during life ceases to be of purely academic interest. Twelve cases are already on record in which diagnosis in the living patient was made possible by the recognition of malignant cells in the pericardial fluid examined by cytological method.

The classification proposed by Mahaim of *polypoid* and *nonpolypoid tumors* has diagnostic and probably therapeutic merit, but it lumps together a wide variety of conditions and includes lesions which, in the strict sense of the word, are not true tumors. Since a consideration of the cell types is of importance, a subdivision into pericardial, myocardial, and endocardial tumors perhaps lends itself to a better understanding of the histogenetic element

PRIMARY TUMORS

Pericardium. At the time of the report of Hochberg and Robinson (1950) describing the successful removal of a large cavernous hemangioma in an 8-year-old girl, 97 observations of primary pericardial tumors had appeared in the literature, mostly *fibromas, angiomas,* and *lipomas* The occurrence of tumors of smooth muscle, a normal component of the pericardium, has also been reported. An intrapericardial cystic teratoma was removed surgically by Beck Incidental to the discussion of tumors springing from lymphatic endothelium, the author (1935) mentions the occurrence of pericardial lymphangioendotheliomas, but others confronted with a similar neoplasm felt that serosal lining cells were a more probable origin and termed the growth *mesothelioma* The concept that this particular type of tumor arises from surface mesothelial cells is now more favorably accepted A wide morphological variation may be exhibited by the pericardial mesothelioma. In general the growth involves large portions of the pericardium and extends early into the adjacent myocardium and even into distant organs When this occurs, it may be difficult to decide which

endocardium, and pericardium may be involved, singly or in combination Leukemic cells are present within the blood capillaries and in the interstitial tissue between the myocardial fibers Actually, the concept of myocardial involvement should be restricted to cases in which leukemic cells are seen outside the lumens of the blood channels The infiltrate may be so scanty as to be detected only under the microscope, or so abundant as to give rise to grossly visible masses A case is on record in which death occurred following rupture of the left atrium, secondary to infiltration of myelogenous cells

Setzu in 1942 was able to gather ten instances of myocardial Hodgkin's disease from the literature and reported an additional case of his own Subsequently, Rast et al. recorded a case with grossly visible involvement of the pericardium by numerous grayish-white nodules, the mediastinum was also involved. Extension of the disease from the mediastinum into the pericardium and myocardium is not rarely seen in routine post-mortem material, and the small number of reported cases does not reflect the actual frequency with which involvement of the myocardium occurs in this condition.

Metastatic Tumors. Metastatic tumors occur from twenty to forty times more frequently than primary malignancies, with an estimated incidence of 3 9 per cent Strong kneading action, rapid blood flow, restricted lymphatic connections, and the metabolic peculiarities of the striated muscle are probably the main features which operate in minimizing the incidence of cardiac metastasis. The relative avascularity of the cardiac valves further explains the rarity of the involvement. All major organs and practically all types of malignancies have been reported as sources, and invasion may occur by embolic, lymphatic, and direct-extension routes. In only one instance was the heart the sole organ involved. (Embolic tumor cells from a primary lung carcinoma were found in the coronary arteries.)

The morphologic aspects of the metastatic nodules are similar to those of similar nodules of other organs and, with the exception of cancerous melanoma, there are no features permitting identification of the primary site from the appearance of the cardiac metastasis. Breast carcinomas, lymphomas, malignant melanomas, and lung carcinoma lead the list of the primary sources in the order given. Yater has found that the right side of the heart is more frequently affected, and Pritchard quoted Kretz's experiment on coronary arterial flow as an explanation of the higher opportunity of embolic tumor cells to lodge on the right than on the left. However, Herbut and Maisel, in a series of 35 cases, found an almost equal distribution of metastatic growths on both sides while, in a series of 101 cases (Scott and Garvin), left-sided involvement was seen to prevail Implantation of tumor cells in the endocardium is rarely mentioned in the literature However, in the series reported by Young and Goldman, there are several instances of myocardial metastasis ulcerating through the endocardium and implanting within the chambers.

CLINICAL ASPECTS

FREQUENCY

Like all bizarre uncommon diseases, tumors of the heart or pericardium are quite unimportant until they become yours to appraise. And, to the afflicted, the lesion is "common" and all-significant Further, because cardiac or pericardial tumors appear but infrequently, it does not follow that they occur "accidentally," i e, without cause Since no physician is likely to see enough of these lesions during the normal course of his observational years, minutely detailed recorded observations on each case encountered are essential for the compilation of data adequate for valid analysis (Table 16-1).

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coma, i.e., cardiac enlargement together with superior-vena-cava–obstruction syndrome, arises chiefly from the frequent location of the growth in the right atrium. In the series of cases reviewed by Mahaim, over half of the sarcomas arose in the right side of the heart, almost equally distributed between the right atrium and the right ventricle. The size of the organ is in general markedly increased, either by massive infiltration or more often by polypoid growths projecting into the chambers. (In one case the heart weighed 2,700 Gm.) As the pericardium becomes involved and the growth extends into adjacent structures, the primary source of the malignancy can no longer be established with certainty.

Endocardium. Endocardial growths constitute nearly 50 per cent of the primary cardiac tumors, but several conditions generally included in the group are not tumors in the true sense. This applies to the so-called hematonodules (blood cysts), a common anatomical finding in the heart valves of infants, which lack pathological significance and are variously considered to be telangiectases or extravasations of blood into the substance of the semilunar cusps or AV leaflets.

Small, villous, comb- or tassel-shaped excrescences of fibroelastic tissue are frequently seen to project on the free borders of leaflets. These formations, known as *Lambl's excrescences,* are not true tumors or even hamartomas. It is generally agreed that they are a manifestation of normal aging, stretching, and wear-and-tear of the collagenous and elastic fibers at the surface of the valvular endocardium.

Endocardial myxoma of the atria (and less frequently of the valves) is the most common primary neoplasm of the heart. Roughly 75 per cent of the 200 cases reviewed by Brewin were in the left atrium and 25 per cent in the right atrium. In almost every instance the growth arises in the region of the fossa ovalis, or its rim, as a pedunculated, lobular, polypoid or villous mass with smooth, glistening surfaces. Constistency may vary from gelatinous to rubbery, and color from yellow-gray to light brown with occasional areas of hemorrhagic discoloration. The microscopic picture is that of a groundwork of amorphous, finely granular or fibrillar material which may or may not stain with mucin stains. A layer of flattened endocardial cells is almost always recognizable at the surface of the mass and a variable number of lymphocytes, plasma cells, and fibroblasts are scattered in the myxomatous tissue. Stellate cells, giant multinucleated cells, delicate blood channels, scattered erythrocytes, hemosiderin and hematoidin pigment are associated microscopic features. Opinions are divided as to whether these tumors are true myxomas or organized thrombi.

Emboli of myxomatous tissue have been found in the extremities, aorta and renal arteries, lungs, and brain. Ribbert has tried to explain the frequent localization of these tumors in the region of the fossa ovalis as evidence of their origin from remnants of myxoid tissue of the embryonic endocardium, but Pritchard, who undertook examination of the interatrial septum in 53 unselected hearts, failed to demonstrate any such remnant.

Since the evidence for or against the neoplastic nature of this peculiar condition is far from being conclusive, the inclusive classification proposed by Husten into (1) end stage of organized thrombus, (2) true myxoma, and (3) doubtful lesion, either thrombus or myxoma, still has its place. All instances the author has encountered seemed to fit in the last category.

Endocardial fibromas are also on record, but since they lack distinctive characteristics, difficulties may arise in differentiating them from organized vegetations or *Lambl's excrescences*

METASTATIC AND SYSTEMIC NEW GROWTHS

Leukemia and Allied Conditions. Although the nature of leukemia and allied diseases is not yet clearly understood, the underlying disease process is that of a fatally progressive, invasive growth of immature cellular elements, from which the myocardium does not escape The myocardium is involved in leukemia more frequently than previously assumed. In a series of 123 fatal cases (Kirschbaum and Preuss), the myocardium was found to display leukemic involvement in 34 per cent of the cases, with the highest incidence (61 per cent) in the stem-cell category. A comparable frequency (36 per cent) was noted by Saphir among 95 leukemias of various kinds. Myocardium,

endocardium, and pericardium may be involved, singly or in combination. Leukemic cells are present within the blood capillaries and in the interstitial tissue between the myocardial fibers. Actually, the concept of myocardial involvement should be restricted to cases in which leukemic cells are seen outside the lumens of the blood channels. The infiltrate may be so scanty as to be detected only under the microscope, or so abundant as to give rise to grossly visible masses A case is on record in which death occurred following rupture of the left atrium, secondary to infiltration of myelogenous cells

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TABLE 16-1. INCIDENCE OF CARDIAC TUMORS

Source	*Institution*	*No of tumors*	*Benign*	*Malig*	*No of autopsies*
Lymburner	Mayo Clinic	4	4	0	8 550
Mallory	Institute of Pathology	3	2	1	20,337
Massey	Madigan General Hospital (U.S.A)	0	0	0	307
Straus and Merlis	U.S. Autopsies, 1938–42	8	..	..	480 331
Walker	University of Michigan	..	.	1	11,101

Nasopharyngeal and esophageal carcinomas, as the author's studies with Maloney and von Fraenkel have verified, metastasize frequently to the heart or pericardium. *Malignant melanomas* often transplant to the intramediastinal structures Half of the victims of *leukemia* disclose infiltrative lesions of the heart or pericardium.

Secondary malignant lesions may be discovered in any part of the heart or pericardium but the endocardial areas seem somewhat less prone to invasion

Carcinoid tumors of the gastrointestinal tract are frequently associated with cardiovascular abnormalities Pulmonic or tricuspid valvular endocardial lesions, ostensibly acquired, are typical accompaniments. Rambo and others have elaborated upon this relationship

CLINICAL RECOGNITION

Tumors of the heart tend to be diagnosed by exclusion. Barring some prominent roentgenographic or clinical manifestations, suspicion of their presence should be deferred until more common causes of cardiovascular disease have been considered. While it is of personal satisfaction to the physician to have diagnosed accurately such an unusual disease, scores of more frequent lesions should not be overlooked Sooner or later, one can always diagnose a cardiac tumor if he is constantly on the alert

Symptoms. Discomfort in the chest may range from *precordial aching* to *painful distress*. A sense of fullness may be experienced in the mediastinum or thorax. Cardiac *palpitation* may occur. *Dyspnea*, with or without heart failure, is not uncommon. If heart failure is present, it tends to be progressive and refractory even to intensive diuretic management. Appearance in a younger individual (up to age 40) of sudden unexplainable heart failure, possibly with some atypical associated findings, can be the initial evidence of cardiac tumors. Intermittent, otherwise inexplicable heart failure, *venous engorgement* of face and neck, and *cyanosis* or *dyspnea*, may be due to the ball-valve action of an obstructive pedunculated intracardiac neoplasm. Such a lesion often causes *syncope, convulsions*, or *coma* because of the significant degree of cerebral insufficiency.

Heart murmurs are sometimes produced by tumors of that organ. In almost all instances, these are due to a *pedunculated* neoplasm, regardless of whether it exerts a ball-valve action Otherwise, gross deformity of normal cardiac chambers is necessary to produce an actual murmur. Distortion of an annulus, a valve, or the entire perivalvular region may result from an extensively infiltrating lesion

Characteristically, the murmur is heard best in the mitral area, but this is by no means universal Variability of its intensity, quality, or pitch would favor the idea of pedunculation, especially if this occurs regularly with *postural changes*. Myxomas of the left atrium most commonly mimic the auscultatory abnormalities of mitral stenosis. This imitation even extends to ballistocardiographic records. Despite painstakingly detailed histories and the employment of all advanced methods of cardiopulmonary diagnosis, there are times when a myxoma of the left atrium has led to the erroneous diagnosis of rheumatic mitral valvular stenosis. In effect, of course, a "stenosis" may be present functionally.

Some authors have indicated that, in one of their patients with an intracavitary atrial tumor, auscultatory signs of mitral stenosis were pres-

ent when the patient was erect and were changed to those of mitral insufficiency when the patient reclined.

Bailey et al. report a patient who had "attacks of dyspnea, paroxysmal tachycardia, and coughing *which were relieved by lying down.*"

While severe prolongation of obstruction of peripheral circulation may progress from intense cyanosis to focal necrosis of the toes, fingertips, or nose, *gangrene* may also develop, or the individual may suffer unexpected *sudden death.* Cardiac tumors with long peduncles are apt to reproduce startling symptoms and signs upon changes in the patient's posture *Morgagni-Stokes-Adams episodes* are apparent at times

Signs. DISTURBANCES OF HEART RATE OR RHYTHM Paroxysmal alterations of heart rate or rhythm occasionally may reveal the presence of a cardiac tumor Similarly, variations in AV or intraventricular conduction can herald neoplastic disease of the heart Sudden and rapid alterations of existing or dominant rhythm, or of conduction are suggestive signs

ENDOCARDITIS A clinical picture *simulating* subacute bacterial endocarditis, but without positive blood cultures, affords a *situation in* which the diagnosis of tumor of the heart should be entertained. Of course, the possibility of lupus erythematosus, collagen disease, amyloid lesions, and the like must also be eliminated.

Electrocardiography. There are no electrocardiographic abnormalities pathognomonic of tumors of the heart or pericardium If ECG variants are found in a patient suspected of having either a primary or a metastatic tumor of the heart or pericardium, the problem of ascribing it to the neoplastic process is often difficult, particularly if the individual is of an age group in which coronary artery disease is probable, or if he has any *evidence of* any organic cardiovascular disease. It is probably safe to assume that an ECG diagnosis of tumor is made exclusively by elimination Unless "strategic" areas of the heart are involved, furthermore, it is not improbable that the ECG would provide no information at all relative to the neoplastic process This is especially true if there are sporadic metastatic nodules in either the myocardium or the pericardium

An unequivocal separation of the ECG tracing of coronary artery disease from that produced by neoplasm represents the most frequently encountered "specific" differential diagnostic problem The ECG inscribed by the neoplastic heart particularly mimics that of coronary artery disease, and especially myocardial infarction. Assessment of the total clinical problem is, therefore, imperative. Appearance of bizarre S-T segment or T-wave aberrations is possible supportive evidence for a diagnosis as unusual as this.

Disturbances of heart rhythm occur as unpredictably with neoplasm of the heart and its protective sac as do the areas of new tissue formation or metastatic implantation. Critical location of the lesions implies instigation of deviant rhythms, whether unimportant in type or potentially lethal in character. So, the gamut from a wandering pacemaker to ventricular fibrillation may be encountered. Details of abnormalities of heart rhythm may be found elsewhere.

Conduction abnormalities also may be produced by the neoplastically diseased heart. Again, as with rhythmic alterations, the site and kind are determined solely by chance Elaboration of the exact findings indicative of the several types of conduction disturbance is to be found in the section dealing in detail with that subject.

Roentgenography. X-ray study of the heart is mandatory in making a cardiologic evaluation of an individual. On such film study, primary tumors may be detected, especially if they are extramural Intracavitary growths or margaric nodules certainly escape detection by this method of examination. Infiltrative types of malignancy would tend to remain obscure upon teleoroentgenography of the heart, but preterminally might be recognizable by, among other things, the gross distortion of normal cardiac contours they have caused. Over-all size in the heart sometimes is increased perceptibly by the tumor. Alteration of the intrathoracic position of the heart seldom is produced

Large tumefactions inseparable, even by angiocardiographic techniques, from the heart most probably are tumors of the heart. The author has seen, however, lesions of this type which, upon surgical exploration, proved to be *noncardiac granulomas,* particularly of the Hodgkin's variety. A ragged appearance of the cardiac outline on posteroanterior films of the

heart may indicate an appreciably advanced degree of cardiac tumor formation. These usually are interstitial in type, representing inexorable *sarcomas*. Because of the rarity of this primary tumor of the heart, details of the clinical findings of the sixth hemangioendothelial sarcoma of the heart reported in the world literature and observed personally by the author, are reported here:

CASE REPORT. A 26-year-old white man entered the hospital in severe congestive heart failure, predominantly left-sided. He was extremely dyspneic and irrational, so that the initial history was obtained from his mother. She stated that the patient first complained of chest pain while overseas in 1943 No further record was available concerning this complaint, and apparently the patient got around adequately until January 29, 1948. At that time, he experienced pain across the entire anterior chest and at both scapular angles. He had marked dyspnea, profound weakness, and poor appetite.

He was treated at a nearby hospital for heart failure, and a secondary diagnosis of subacute bacterial endocarditis was made. Sulfonamide therapy, followed by administration of penicillin and streptomycin, was employed with no apparent benefit, although the patient's condition seemingly improved following a short course of the last-mentioned drug His illness continued for 4 weeks and he was then sent home for a brief period before being admitted to Madigan General Hospital on March 2, 1948

On entry there the patient presented marked pallor and obvious dyspnea His lips, tongue, and skin generally were extremely dry and his temperature was 105 2°F. He was mentally disoriented, but passively cooperative

The heart was regular in force, rate, and rhythm, with a sinus tachycardia of 120 per minute There was gross enlargement of the heart, so that the apical impulse was felt in the 6th interspace between the left anterior and midaxillary lines There was a grade 4 coarse and blowing murmur over the pulmonic area, and the 2d aortic sound was markedly accentuated The other valvular areas were normal Arterial blood pressure averaged 110/70 mm Hg supine The lungs revealed coarse rales in both bases posteriorly, especially the left

During this acute episode, he was treated with oxygen, morphine, digitoxin, and mercuhydrin, to which he responded satisfactorily. Five consecutive blood cultures were obtained, following these penicillin was administered in doses of 300,000 units every 3 hr intramuscularly A satisfactory response was obtained within 24 hr but the penicillin was continued for 1 month None of the blood cultures became positive. Blood-pressure readings ranged between 104/70 and 90/60 mm Hg between March 24th and April 8th, the latter readings obtaining from April 3d onward The apical pulse continued at a rate of 130 per minute

Improvement was progressive to a point at which the patient became moderately ambulatory until April 5th. On that date, at 10 o'clock, he became very weak, complained of thirst, and exhibited a violet hue over the upper half of the thorax anteriorly. His face remained pallid, with no cyanosis. The liver was enlarged, extending down 6 to 8 fingerbreadths and filling the entire epigastrium. The patient did not complain of pain He suffered from increased venous pressure. Mercurial diuresis was effective in relieving some of the liver congestion On April 6th, he had an unalleviated acute failure of the right heart, this was unresponsive to protracted energetic treatment, and he died quietly on April 8, 1948

The urine was entirely normal White blood cells varied from 13,250 on admission to 20,150 just before death. The sedimentation rate (Wintrobe method) varied from 42 to 53 mm/hr The hematocrit reading varied from 37 to 44 Nonprotein nitrogen and icterus index were normal

X-ray examination showed a "mitral configuration with marked prominence in the region of the pulmonary arteries and conus" (Fig. 16-5A) Generalized cardiac enlargement was evident

At autopsy the following essential gross findings were seen· The lips were blue A few petechiae were seen over the left anterior chest and the lower sternal region. There was no clubbing of the fingers The nail beds of the fingers were cyanotic and contained no splinter hemorrhages In the peritoneal cavity, there was 600 ml of amber, blood-tinged fluid The left pleural cavity contained 1,000 ml of bloody fluid and the right about 600 ml The left lung weighed 560 Gm, the right 840 Gm. The tracheobronchial lymph nodes were normal The pleural surfaces of both lungs were covered with many round, slightly umbilicated, reddish-purple hemorrhagic nodules 0 5 to 3.5 cm in diameter. All lobes were firm and noncrepitant. Marked congestion was evident and the bronchi exuded hemorrhagic mucus The pericardium was fibrotic and densely adherent to the epicardium, completely obliterating the pericardial sac and averaging 3 mm in thickness The diaphragmatic pericardium was studded with many *purple tumor nodules* averaging 2 5 cm in diameter The heart measured 17 cm transversely, 22 cm vertically, and 11 cm in the anteroposterior diameter With the pericardium, it weighed 2,030 Gm The coronary arteries were small and pliable with marked narrowing of their lumens, no obstruction

was noted The myocardium was firm, dark purple-red, and bloody throughout. There were many *diffuse, confluent tumor nodules* (some centrally necrotic) in all areas but more on the right side and in the upper 1 5 cm of the interventricular septum. Large areas of the endocardium of the right ventricle and atrium and about the tricuspid valve were invaded by the tumor The purple, hemorrhagic, neoplastic nodules had amalgamated the heart and pericardium so that the myocardium was 2 5 cm thick on the right side and 3 cm thick on the left, the outer 2 cm of this side consisted of muscle The wall of the apex of the right ventricle was 5 5 cm thick; that of the pulmonary conus was 4 5 cm thick The distance from the base of the tricuspid valve to the right apex was 7 5 cm, from the base of the mitral valve to the left apex, 8 5 cm The chordae tendineae and papillary muscles were hypertrophied and bloody on section Subendocardial hemorrhages were scattered throughout. The valve circumferences were normal All the tumor nodules were strikingly hemorrhagic and blood had *infiltrated into all the* cardiac tissues. The aorta was normal throughout as were the major aortic and pulmonary branches. The abdominal viscera were congested.

Microscopic findings were as follows. Sections of the lungs showed marked congestion A few small nests of tumor cells were found lying loosely in the parenchyma without any pattern These cells were irregular, with scant eosinophilic cytoplasm and irregular hyperchromatic nuclei Sections of the heart stained with hematoxylin and eosin showed many varying-sized spaces *forming* what appeared to be poorly formed vascular *channels* In many places, these spaces resembled young capillary tubes These channels were lined by a loose network of immature cells resembling endothelium in many places The cells varied in size and shape, had a small amount of pale eosinophilic cytoplasm and hyperchromatic irregular nuclei which had a fine granular network supporting one to three central or eccentric nucleoli. The nuclei filled a large proportion of the cell Some of the nuclear granules were coarse and heavily stained. Some of the cells had phagocytized erythrocytes. Many of these cells were closely grouped, forming thin strands connecting larger ones. Erythrocytes had engorged many vascular spaces to form solid areas of hemorrhage, some of which were centrally necrotic. No striated muscle cells were found in the tumor areas, which had completely *replaced* the myocardium. The section taken from *the left* ventricular wall at the junction of the *tumor tissue* and the myocardium showed the myocardial fibers to be in various stages of *degeneration, with* infiltration of individual tumor cells Here the tumor was sharply delineated from the myocardium There were a few isolated atrophic groups of muscle fibers present in the tumor area. Away from the tumor process, the remainder of the myocardium was *normal*

Fluoroscopy. Evaluation of cardiac *dynamics* is an indispensable part of the heart *examination*. Detection of an extramural myocardial mass may materialize first by this method. The heart tumor should be differentiated from a pericardial cyst, a ventricular aneurysm, and an extracardiac lesion. Solid tumors of the

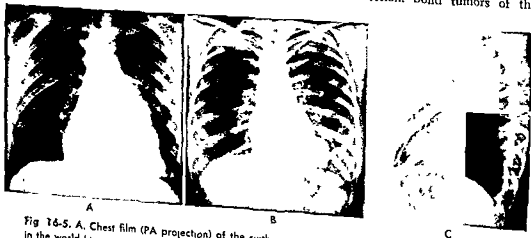


Fig 16-5. A. Chest film (PA projection) of the sixth primary hemangioendotheliosarcoma reported in the world literature. Note especially the totally irregular margin of the left border of the heart, deforming the pulmonary salient (i e, pulmonary artery–pulmonary conus–left atrium region) as well as the left ventricular segment (From Glassy and Massey, Amer J. Med. 1950) B. Cyst of the pericardium, grossly deforming the left ventricular segment of the left cardiac border. It simulates, among other lesions, left ventricular aneurysm. The left lateral projection (C) indicates its position in the anterior mediastinum.

heart tend to differ fluoroscopically from aneurysmal lesions in that the former do not pulsate, except synchronously with ventricular systole, and certainly *there is no expansile pulsation.* Differentiation of cardiac tumors from pericardial cysts or from intimately contiguous extracardiac solid lesions usually cannot be accomplished through fluoroscopy.

Infiltrative neoplasms of the myocardium may be inferred by observing a ragged cardiac contour, especially if it is left-sided, i.e., on the pulmonary salient or on the left ventricular segment. Intracavitary primary tumors of the heart, or metastases to the myocardium, are not discernible by fluoroscopic visualization.

Pneumopericardiography. Intrapericardial injection of air has been shown to be, at least theoretically and on several occasions, a practical method for demonstrating tumefaction of the cardiac surface.

Radiologic Opacification Techniques. Lehman et al point out that "selective" angiocardiography, employing the direct placement of the dye into the outflow tract of the right ventricle, probably would be the procedure of choice in order to demonstrate an intraatrial myxoma, for example One could expect a satisfactory demonstration of such a tumor in a person with that provisional diagnosis.

Failing in that procedure, and provided the patient has a good-sized left atrium, the most preferable alternative procedure would be that of direct (needle) opacification of that chamber, to attempt demonstration of the existence of an intraatrial mass.

Ventriculography by the technique of Lehman et al could demonstrate left intraatrial tumors only if there is severe mitral insufficiency, because otherwise the dye is propelled forwards instead of backwards. To date, intraventricular tumors have not been demonstrated by this method of direct ventriculography.

PRIMARY TUMORS OF THE MYOCARDIUM

Varieties. There are many varieties of primary myocardial tumor. The commonest are described below

RHABDOMYOMAS. *Rhabdomyomas* are primary myocardial, usually ventricular, tumors comprised of striated muscle fibers and also known as *myoma striocellulare.*

Rhabdomyomas are found most often in infancy. Because of their frequent association with (von Gierke's) *glycogen-storage* disease, much interest has centered around determination of their origin. *Tuberous sclerosis* is also found in half of the patients with rhabdomyomas. This interesting disease helps to uncover cardiac rhabdomyomas more readily because of the more apparent neurologic symptoms and signs Multiple renal tumors and adenoma sebaceum tend to be associated with the rhabdomyomas. Since there is some tendency for them to localize as nodules near the apex, it may be possible to identify an irregular left ventricular margin on the roentgenogram and thus to make a provisional diagnosis. The tumors tend to blend histopathologically into adjacent normal myocardium.

Because of its obscure pathogenesis, perhaps the term *rhabdomyoblastoma,* indicating the existence of a tumor whose cells tend to differentiate into striated muscle cells, would be more applicable.

RHABDOMYOMYXOMA. *Rhabdomyomyxoma* is the term used to indicate a tumor comprised of both myxomatous and rhabdomyomatous tissue All these tumors are benign and theoretically potentially amenable to surgical intervention.

MYXOMAS. *Myxomas* are the most common primary neoplasms of the heart. Some physicians regard them as deriving from an organized thrombus and are reluctant to attribute a neoplastic character to them. Others feel they are, indeed, true tumors arising from embryonal mucoid tissue-rests. Their gross consistency is soft and gelatinous, resembling the mucinous connective tissue normally found in the umbilical cord

Predominantly left-sided (of the heart) in origin, the myxoma is typically a lesion of the left atrium, but has been found to originate at the base of the left atrium, *in the left* ventricle, or occasionally in any of the other chambers of the human heart. Controversial tumors of the heart valves have been identified upon occasion as myxomas.

LEIOMYOMA. Leiomyomas of the heart are benign tumors constituted of unstriped muscle fibers Anaplastic instances may be referred to as *leiomyoblastomas.*

FIBROMA. Fibromas are benign, solid tumors of myocardium which are composed exclusively of mature connective or fibrous tissue. In the cardiac wall, these do not undergo the cystic degeneration often displayed by uterine fibromas.

MESOTHELIOMA Mesothelial tissue, derived from the mesoderm to produce pericardium, pleura, and peritoneum, provides the cells which comprise the tumor known as mesothelioma Flat cells of mesodermal origin lining the coelom, or body cavity of the embryo, are the basis for the term coelothelioma, synonymous with mesothelioma Mesotheliomas most often develop in the area of the AV node Their location at the base of the interatrial septum, around the node, and at the beginning of the bundle of His, makes them apt to cause either incomplete or complete heart block

OTHER TUMORS. *Lipomas, xanthomas, teratomas*, and other less common primary benign tumors may occur in the myocardium Practically, i e, therapeutically, these have the same importance as the other neoplasms described above, with the exception of the debatable myxoma

Benign tumors involving the basic elements of the lymphangioendothelial system are seen infrequently, *angiomas, hemangiomas, lymphangioendotheliomas,* and *angioreticulomas.*

LEUKEMIC INFILTRATION OF THE HEART. Infiltration of the myocardium is not an uncommon circumstance in cases of leukemia, although essentially no work has been done to correlate the clinical and electrocardiographic manifestations with those of the necropsy examination. The leukemic cells which may be lymphogenous or myelogenous are found in both the capillaries and in the myocardial interstitial tissue Several cases in the literature have disclosed cardiac involvement sufficient to produce incomplete heart block; only one instance of complete AV dissociation has been described.

While both clinical and electrocardiographic evidence of cardiac abnormality may exist in leukemic individuals, these usually (and perhaps logically) are attributed more readily to rheumatic, arteriosclerotic, or other potential causative factors The electrocardiographic patterns depend upon the individual peculiarities of the leukemic infiltration and obviously exclude the existence of a pathognomonic tracing

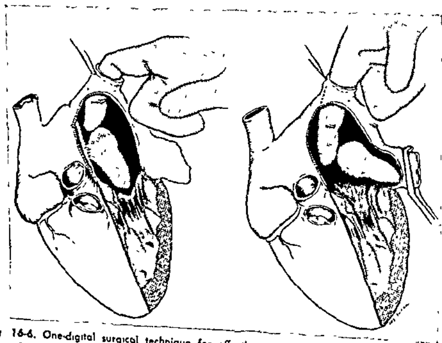


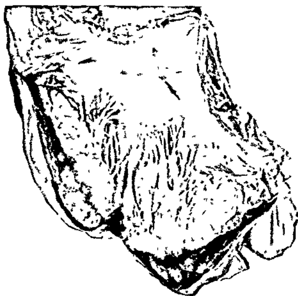
Fig 16-6. One-digital surgical technique for effecting removal of pedicled intraatrial tumor. (From Bailey et al, Surg Clin No Amer., 1951)

Treatment. PRIMARY BENIGN TUMORS. Since surgical techniques have progressed to the degree of perfection they display today, it is desirable to diagnose a tumor of the heart as promptly and as precisely as possible This may allow suitable surgical survey and possible curative excision of several of the most common tumors, both intracavitary and intramural. Successful removal of a 3½-lb primary lipoma of the myocardium was reported by Maurer (1952). Beck had done a similar, pioneering excision (1942). (Fig. 16-6.)

PRIMARY MALIGNANT TUMORS While it is conceivable that effective surgical excision of a circumscribed, delimited malignancy of the myocardium may be achieved, this remains to be demonstrated convincingly. Nichols et al have shown that recurrent, slow-growing tumors of the heart may be managed in just such a fashion, as long as their site is not critical.



A



B

Fig. 16-7. A Margaric nodules, secondary to malignancy of the urinary tract, appearing in the ventricular myocardium. B. Two tumor vegetations on a mitral valve The one in the center is near the free border of the cusp, while the one on the right is at the base of the cusp These neoplastic endocardial implants were metastatic from a bronchogenic carcinoma, and their appearance on the mitral valve seems to be the first reported instance of secondary lesions involving that structure (From Coller et al., Am. J. Clin. Path., 1950)

SECONDARY TUMORS OF THE MYOCARDIUM

Varieties. Metastatic carcinoma invades the myocardium with appreciable frequency, developing as discrete *nodules epicardially* and *intramurally*, and causing *miliary infarcts* and *coronary arterial emboli*. It may occasionally develop in the form of *carcinomatous lymphangitis* As stated previously, these lesions may develop in any area of the heart, although there is little tendency for the endocardium to be involved. Recently, very striking photographic examples of intravalvular metastases have been displayed, even though the incidence there is very low. Right-sided metastatic cardiac lesions predominate (Fig. 16-7A and B)

Infiltrative lesions make their appearance via lymphatic routes or by direct myofibrillar invasion *Hematogenous spread* tends to follow ulceration or rupture into a venous channel, such as a pulmonary vein or the inferior vena cava. Each particular case is individualized in this respect.

Hodgkin's disease, malignant lymphoma, leukemia, myeloma, lymphosarcoma, and reticulum-cell sarcoma comprise the vast majority of the infiltrative processes Unique instances of other systemic diseases producing myocardial infiltration have been reported

In the author's review of histopathologic material (from King County Hospital, Seattle, School of Medicine), the following were among the secondary tumors of the heart:

Case	*Primary*	*Secondary*
F L	Carcinoma, bronchial cleft	Myocardium
A T	Carcinoma, rectum	Epicardium
W. S F	Squamous cell carcinoma, lung	Myocardium
E G	Sarcoma of foot, type not noted	Myocardium
J. E H	Epidermoid carcinoma, buccal mucosa	Myocardium
G L	Malignant melanoma	Myocardium
M J B	Carcinoma, adrenals	Myocardium
L. L.	Adenocarcinoma, thyroid	Right atrium
D McD	Squamous cell epithelioma	Myocardium

Treatment. Since the secondary lesions represent only a phase of widespread disease, the proper treatment obviously remains that of the basic process

Other than symptomatic relief of pericardial effusion with or without cardiac tamponade because of associated pericardial extension, there is nothing specific to offer in the way of effective therapeutic measures directed against the myocardial malignancy Urethane, nitrogen mustard, triethylene melamine, radioactive phosphorus (P^{32}), or radioactive gold (Au^{198}) have been employed with unpredictable and equivocal results

TUMORS OF THE PERICARDIUM

Benign. Fibromas, lipomas, and angiomas may involve the pericardium, thickening or bulging it, but usually without producing clinical symptoms If diffuse, any of these lesions might cause constrictive symptoms Ordinarily, the pericardial space is preserved in their presence

Teratomatous cysts, derived from the region of the third branchial arch, characteristically are attached to the anterior (ventral) aspect of the pericardium, apparently having been drawn down into the thorax during the embryonic descent of the heart In at least two instances, they have been found within, and removed from, the pericardial cavity (Neugebauer, Beck) Most such teratomas fortunately are benign

TREATMENT Surgical removal of a benign tumor of the pericardium has never presented unusual difficulty. The technique consists of merely removing the involved portion of the pericardium with a sufficiently wide margin to ensure a complete excision.

Malignant. These lesions tend to be separated clinically into (1) those which remain in, and extend within, the pericardial substance alone, and (2) those which tend to invade the heart Mesotheliomas are likely to follow the former pattern of behavior while sarcomas usually extend directly into the contiguous myocardium, producing a "lumpy" cardiac border on the teleoroentgenogram (Fig 16-5A)

With the former type of lesion, voluminous pericardial effusion is common, being serous at first, then hemorrhagic It produces symptoms and signs of cardiac compression, recurs rapidly after paracentesis, and frequently contains tumor cells Cytopathologic examination of sedimented debris from the aspirated fluid often reveals the nature of the process.

When the heart is invaded directly, obstruction of either vena cava is common, while symptoms of cardiac constriction may occur due to the woody encasement of the ventricles. Signs of congestive heart failure may develop because of extensive malignant cellular invasion and eventual total replacement of the normal muscle fibers. The successful surgical treatment of such lesions has not yet been reported

CYSTS OF THE PERICARDIUM

Incidence. Pericardial cysts are rare, although not as unusual as the sparse reports of 103 cases up to 1957 would suggest. Lenkert was the first to report such a lesion (1928). With the mass roentgenographic surveys now being made, pericardial cysts should be recognized with increasing frequency.

Classification. Cysts of the pericardium may be designated as acquired or congenital Acquired cysts usually amount to pericardial enclosures of a pocket of exudate Congenital pericardial cysts often are referred to in other terms, e g, as pericardial diverticuli, pleuro-

pericardial cysts, pleurocoelomic cysts, pericardial coelomic cysts, or pericardiophrenic angle cysts.

True pericardial cysts are semitransparent, thin-walled sacs attached to the pericardium; they may contain up to a liter of serous, watery transudate. Apparently, they are composed of tissue resembling pleura and pericardium. Drash and Hyer propose that they be known as mesothelial mediastinal cysts. The walls contain collagenous connective tissue lined by a single layer of cells, characteristically flattened, but which may assume a cuboidal "epithelial" appearance.

Pathogenesis. These cysts generally are believed to be of congenital origin whether one accepts Lambert's theory of failure of complete coalescence of the several mesenchymal lacunae into the primitive pericardial coelom, or Lillie's presumption of "pinching-off" of diverticulum-like structures (such as the ventral parietal recess) which normally appear in the development of the pericardium.

Clinical Importance. Of themselves, pericardial cysts are of minor clinical importance, but often they involve neat, if difficult, differential diagnosis. Lesions from which these intrathoracic cysts must be differentiated include (1) extrapericardial fat pads, (2) esophageal hiatus hernia, (3) partial diaphragmatic eventration, (4) cardiac aneurysm, (5) cardiac tumor, (6) teratoma, (70) lipoma, (8) lymphangioma, (9) secondary hydatid cysts, and (10) subphrenic abscess.

Symptoms. Clinically, these cysts are always benign and regularly produce no symptoms except (occasionally) vague thoracic pain Undoubtedly, there is always possibility of such enlargement as to encroach upon the respiratory reserve and cause shortness of breath and coughing.

In more than one-half of the cases, they appear in one of the cardiophrenic angles, usually the right, and if large, may lose their rounded outline and become flattened due to the effect of gravity. Some are attached by pedicles and may change position, as well as shape, with alterations in posture: a diagnostic feature. Occasionally they exhibit luminal communication with the pericardial sac. Friedberg then uses the term *pericardial diverticulum* or "pseudocyst."

Diagnostic Methods. Nearly always the presence of the mass is detected incidentally through an x-ray observation (Fig 16-5B and C). Additional means of specifically diagnosing the presence of a pericardial cyst include (1) further roentgenographic studies including oblique views and laminograms as indicated, (2) angiocardiography; (3) pneumoperitoneum; (4) observation of the patient over a period of months; (5) Funch's method of aspiration and injection of air; and (6) thoracotomy (the only certain method of diagnosis).

Differential diagnosis between two easily confused mesodermal lesions is presented below, based upon findings evident at thoracotomy.

Pericardial cyst	*Lymphangioma*
Simple structure, i e, unilocular	Complicated structure, i e, multilocular
Walls, thin (mesothelial)	Thicker walls, contiguous adherence
Blood supply from pericardium	Blood supply from pericardium and elsewhere

7

Traumatic heart disease

Myocardial Alterations Caused by Physical or Chemical Agents

C. GEORGE TEDESCHI

Clinical Aspects of Traumatic Heart Disease

RAY WILLIAM KISSANE

Air Embolism

RAY WILLIAM KISSANE AND STEWART M. ROSE

MYOCARDIAL ALTERATIONS CAUSED BY PHYSICAL OR CHEMICAL AGENTS

PHYSICAL INJURIES TO THE HEART

Traumatic Injury. Moritz (1942), in his discussion of the mechanisms of injury by physical violence has made clear the distinction between *primary* (or *direct*) and *secondary* (or *indirect*) myocardial injury *Primary injury*, functional, structural or both, was defined as that resulting from a force directly applied or transmitted to the heart The designation *secondary injury* was given to cardiac disturbance resulting from disruptive or functional changes produced elsewhere in the body by a traumatizing agent

PRIMARY TRAUMATIC INJURY. The force responsible for a direct injury can be a *penetrating* wound (such as that resulting from a flying missile, or a slender, rigid object) or a blunt impact Since a missile travels at much higher velocity, it ordinarily causes much more extensive injury than a stab wound The latter tends to close when the force is withdrawn and this explains why the victim may survive long enough to undergo surgical repair of the defect It has been indicated that the clotted blood filling the intramyocardial wound is slow to resorb and that fibroblastic proliferation is seldom well under way before 2 weeks have elapsed, however, Moritz (1953) has seen epicardial and endocardial fibrous plaques at the sites of entrance and exit of a penetrating wound, a month after its infliction, in the absence of any other detectable alteration.

The most important complications of a penetrating myocardial wound are shock, hemorrhage, and infection If the associated *pericardial* defect is large enough, the escaping blood tends to collect in the pleural cavities, if blood does not escape from the pericardial cavity rapidly, it collects in the pericardial space and the consequent rise in intrapericardial pressure will lead to cardiac tamponade.

Commotion, contusion, and *laceration*, according to the strength of the disruptive force, are the main effects of a blunt precordial impact. *Cardiac commotion*, by definition, indicates a disturbance in function not accompanied by structural alteration There are records of the death of human subjects subsequent to blunt injury of the chest, in these cases, death was found to be due to heart failure, despite the absence of structural damage Transient disturbances in cardiac function following impact on the chest have been also reported by several investigators, both in man and *in experimental* animals Schlomka and Schmitz, from animal experimentation, concluded that the cardiac disturbance caused by commotion is secondary to reflex coronary vasoconstriction and myocardial ischemia This concept is well substantiated by the demonstration of dissem-

inated ischemic necrosis in traumatized human hearts and by the finding of foci of myocardial necrosis in animals subjected to nondisruptive cardiac impact (Kastert). The observation that rabbits with cholesterolosis of the coronary arteries are less tolerant to blunt injury of the chest might be correlated to the observation that even a minor precordial trauma can precipitate cardiac failure and death in individuals with lesions of the coronary vascular bed.

The term *myocardial contusion* applies to the condition characterized by escape of blood between the myofibrils (without any other appreciable structural alteration) which results from a blunt force directly applied or transmitted to the heart. Rise of intracapillary pressure and stretching or distortion of the walls of blood vessels are the main causes of the hemorrhage

Aside from penetrating injury, a fall from a height is the most common cause of *laceration* of the heart. The sudden distortion and compression of the organ produces a rise of pressure in the cardiac cavities and causes the myocardium to burst at the point of greatest strain and least resistance, in general the right atrium or ventricle. The defect in the continuity of the tissue may be so small as to be barely detectable with the naked eye or so extensive as to result in rupture of the heart. Moritz and Atkins have produced evidence indicating that the hydrostatic force incident to the sudden compression of the heart by the bony structures of the thoracic cage is the main factor which operates in disrupting the myocardium.

Since in the first four or five decades of life the thoracic cage is usually sufficiently plastic to permit distortion without fracture, cardiac commotion, contusion, and laceration are more likely to occur in the absence of disruptive bony injury On the other hand, a rigid, more easily fractured, thoracic cage is an important factor in protecting the heart from a blunt force

Myocardial contusions and lacerations may occur during rhythmic manual compression (of the heart) of the type which is employed for resuscitation of the heart Tedeschi and White have shown that the fibrillating heart is more likely to be injured than the normally beating heart because it is relatively rigid

SECONDARY TRAUMATIC INJURY. The normal myocardium is not permanently affected by stresses following a disruptive trauma elsewhere in the body. However, the same injury may represent a potential threat to a heart already handicapped by an organic disorder The frequency with which a fatal attack of acute myocardial hypoxia is initiated during exertion points out the danger of a pressor episode in an organically diseased heart and even in a heart which is in a borderline condition compatible with an apparent state of health.

As a result of a mechanical disruption of tissues, several types of emboli may penetrate the circulatory system and reach the chambers of the heart. Blood stasis, tissue edema, and muscular inactivity are frequent sequelae of traumatic injury and these conditions predispose to venous thrombosis and embolism Emboli of hepatic cells within the cardiac chambers may be seen in disruptive injury of the liver. Entrance of air into the circulating blood through patent veins, and of fat droplets from disrupted skeletal or extraskeletal fat, are other possible sources of embolism. Fatal occlusion of the anterior descending branch of the left coronary artery by a small amount of fat was seen by the author. In this case the patient was the victim of a tornado and died suddenly 24 hr after an apparently mild injury to extraskeletal adipose tissues. There was associated pulmonary embolism which had given only a minimal degree of functional disturbance, namely, a mild degree of dyspnea during the interval between injury and death

Injury Caused by Changes in Atmospheric Pressure. Whenever the human organism undergoes a sudden, marked reduction in atmospheric pressure, the change in tension releases some of the gases from solution, and air bubbles, mostly inert nitrogen and carbon dioxide, enter the blood stream giving rise to one form of air embolism In fatal cases, large air bubbles can be found in the right heart soon after death, although other cardiac alterations will be absent.

Blast Injury. Blast injury is the disruptive effect in the tissues resulting from a sudden change in pressure brought about by the force of an explosion. The force may be transmitted through either air (air blast), water (immer-

sion blast), or rigid structures (solid blast) The walls of the hollow viscera, including the heart, are particularly susceptible to this type of injury, which is often seen when there is little or no external evidence of trauma.

Hypothermal and Hyperthermal Injury. HYPOTHERMAL. Circulation fails when the temperature of the blood is reduced to the vicinity of 20°C. In individual cases, port-mortem examinations have disclosed right heart dilatation and pulmonary edema Hoff and Nahum have described the use of metal thermodes for the investigation of the local effects of hypothermal injury Taylor et al. have produced transmural muscle necrosis by using an instrument cooled to −60°C with expanding carbon dioxide.

HYPERTHERMAL Those systemic disturbances caused by cutaneous burns may result in a variety of secondary disorders mostly due to hemoconcentration, low blood pressure, and the systemic hypoxia of secondary shock. Although the effects of the impact of the generalized disturbance are most apparent in the kidneys, liver, and adrenals, degenerative changes in cardiac myofibrils and endocardial mural thrombosis have been observed in fatal cases

In systemic hyperthermia, a general rise in the temperature of the circulating blood above 42.5°C results in generalized vasodilatation, reduction in effective blood volume, and changes in respiration: first stimulation and then cessation Cardiac dilatation and the structural deterioration of the myofibrils explain the impairment of cardiac efficiency and the rapid pulse which occur under these conditions

Electrical Injury. The path of a current through the body tends to follow the most direct route between the sites of entrance and exit The principal conductors of the electric current are the fluids, and most of the current travels along the vessels In flowing through the tissues, the current may (1) produce destruction of cells by heat or electrolysis, (2) stimulate strong muscular contraction, or (3) inhibit the function of vital centers that lie in its path The nature and degree of harmful effects are dependent upon a combination of conditions, mainly the duration of the current, its path, and its amperage and voltage. The mechanism of death from electricity is still a matter of much dispute Some consider that it is due to cardiac paralysis, others to paralysis of the respiratory centers When a low-tension current passes through the heart, fibrillation occurs On exposure to high-tension current, the function of the heart stops abruptly. Pathognomonic alterations take place in neither case. Petechial hemorrhage in the pericardial membranes results from the vascular damage of acute systemic hypoxia.

The effect of alternating current, countershock, and condenser-discharge countershock on the fibrillating canine heart have been investigated by Tedeschi and White. Both epicardial and myocardial damage was found at the site of application of the electrodes. The damage was manifested initially by epicardial fibrinous hemorrhagic exudation, necrosis of subepicardial fat, fragmentation and necrosis of the myofibrils, and inflammatory reaction. Pericardial adhesions and superficial myocardial fibrosis were observed subsequently in the animals that survived Alternating current was productive of more severe changes than condenser-discharge current and the injury was not influenced by the type of electrode surface using either type of current.

Radiation Injury. The median lethal dose for different cells and organisms varies widely, and a wide range of radiosensitivity exists among cells of a single type. Nevertheless there are average differences in cell resistance and sensitivity to radiation of a magnitude large enough to be of practical significance With respect to vulnerability to radiation, a classification has been proposed by Warren, according to which the tissues are divided into three main categories: (1) To the *radiosensitive* category he allocates those tissues which become seriously injured on exposure to 2,500 r or less (2) The *radioresponsive* category comprises those tissues which suffer serious injury on exposures ranging from 2,500 to 5,000 r. (3) The *radioresistant* tissues are those which become damaged on exposures to more than 5,000 r. The myocardium belongs in the last category The only significant cardiac changes observed by Liebow et al among victims of the Hiroshima and Nagasaki atomic bomb explosions were subendocardial and epicardial petechial hemorrhages, occasional infiltration

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lomas. However, Fawcett, in a critical attempt to reassess the problem, studied the incidence of this picture as it occurred one year prior to and one year following the advent of sulfonamide chemotherapy and found an almost identical number of cases in the two groups. Further caution in approaching the subject is suggested by the failure of Merkel and Crawford to demonstrate myocardial changes in five patients whose death had been attributed to sulfonamide hypersensitivity The author has had two comparable experiences.

CLINICAL ASPECTS OF TRAUMATIC HEART DISEASE

NONPENETRATING INJURIES

Borch (1676) published the first probable case history of nonpenetrating cardiac trauma. An 8-year-old boy had fallen between a table and a footstool, bruising his chest He died 4 months later, and the necropsy revealed a large right atrium which was described as "pale, yellow, and nearly decayed" These pathological findings were considered to be the result of trauma However, this explanation of their origin is open to doubt

Akenside (1764) reported what is probably the first unquestionable case A 14-year-old boy complained of chest pain and developed a cough with hemoptysis immediately after being struck between two ribs by the edge of a plate. He lived about 6 months thereafter. Following his death, the necropsy revealed an area of necrosis the size of a half-crown on the left side of the heart, and a totally adherent pericardium

Historical Considerations and Incidence. Warburg reviewed the literature and found that, from 1676 to 1868, only 27 cases of cardiac trauma were reported The impressive work of Fischer was published at that time and, while he collected 76 case histories, only seven described myocardial contusions and none traumatic cardiac rupture The number of cases reported has greatly increased since 1900, but still many clinicians and pathologists consider the condition rare. Fifty unselected consecutive victims of fatal automobile accidents were examined by Leinoff, and he found that eight (16 per cent), showed microscopic evidence of cardiac damage In a review of 1,000 necropsies of contusion of the chest, Urbach found that 185 (18.5 per cent) showed injury to the heart.

Method and Mechanism of Injury. Urbach lists these mechanisms of injury in their order of frequency.

1. Falls from a high place
2. Blows from the fist
3. Kicks
4. Blows by heavy objects or wagon tongues
5. Butting by animals

These causes, however, do not apply to a machine age, and during the past 40 years most blows to the chest have been caused by striking the steering wheel or instrument panel of an automobile, or the back of an automobile seat Blows received on the anterior or left side of the chest most frequently produce cardiac injury. The force of these blows need not be sufficient to fracture the bony cage or cause more than minor contusion to the chest wall The heart may also be injured by compression of the chest from various angles, most frequently from front to back.

Pericardial and Epicardial Injury. The factors that predispose the pericardium to injury are anatomical, such as attachment to the central tendon of the diaphragm, fixation by the sternopericardial ligament to the inner side of the sternum, frequent fusion with the pleura, irregularity of thickness, amount of fat, and elasticity Blows that varied in intensity from that of a hard rubber mallet to a 10-lb sledge hammer were struck on the chests of 19 anesthetized dogs, and the most frequent injuries to the pericardium were pericardial and epicardial hemorrhages and tears These lesions, when uncomplicated by myocardial contusion, are usually due to relatively moderate blows In 26 human cases that came to necropsy as the result of severe extracardiac injury with only mild to moderate chest trauma, *subpericardial hemorrhage* occurred in all but two cases, *pericardial hemorrhage* in ten, and small pericardial or epicardial tears in four. All these patients died within 2 weeks subsequent to injury and, in the remaining twelve who survived from 6 to 18 months, subpericardial fibrosis occurred nine times These subpericardial hemorrhages are usually anterior and near

by inflammatory cells, fatty change in one instance, and focal myocardial necrosis in another. Thibaudeau and Mattick autopsied patients dying from 2 days to 1 year after radiation treatment that included exposure to the heart. They noticed changes in the myofibrils ranging from granular or vacuolar degeneration to hyaline change and necrosis with occasional slight interstitial fibrosis and sometimes round-cell infiltration. Although radiation injury of the myocardium, as elsewhere in the body, has no specific features, the combination of aseptic necrosis, fibrosis, and obliterative endoarteritis is considered sufficiently characteristic to warrant identification (Warren).

CHEMICAL INJURIES TO THE HEART

Poisons may injure by local action at the point of entry, by their action upon distant organs following absorption, or by a combination of both mechanisms. Local myocardial injury by chemical agents is prevented in the human being by the particular situation of the organ. In experiments on the exposed heart, local application of phenol has resulted in death within 1 hr, probably due to the systemic effects of the substance. Myocardial necrosis was produced by means of local application of sponges saturated with formalin, or by intramyocardial injections of solutions of mercuric chloride (5 per cent) and silver nitrate (20 per cent).

Among the poisons with systemic effects, similar myocardial lesions are produced by a wide range of substances, and perhaps the common underlying factor is interruption of the oxygen cycle either outside or within the cardiac tissue.

In anesthetic death and in death caused by hypnotics and sedatives of the barbiturate group, hypoxia is brought about by depression of the respiratory centers

Interference with normal respiratory function, secondary to pulmonary edema and hemorrhage, is the mechanism operating in the hypoxic state that results from exposure to phosgene, chlorine, sulfur dioxide, and other irritant gases.

Hemolysis, as it occurs in arsine intoxication, also results in a condition of anoxemia, and a similar mechanism operates in the anoxemic death that ensues after exposure to bone-marrow depressants, such as benzol.

Inactivation of the respiratory enzymes of cardiac tissue follows poisoning by cyanide compounds.

Oxygen deficiency is a major aspect of carbon monoxide poisoning and myocardial necrosis may be one result. Ehrich et al. exposed dogs to a concentration of carbon monoxide greater than 75 per cent for 15 min to 1 hr and found myocardial necrosis, hemorrhage, and early deposition of calcium salts Comparable myocardial alterations, particularly in the papillary muscles, were observed in human beings dying of carbon monoxide poisoning. Inflammatory changes, interpreted as secondary to the muscle necrosis, were also noted The sudden occurrence of coronary thrombosis and of myocardial ischemic necrosis weeks or months after recovery from the poisoning has been observed.

As an example of the type of injury caused by the mineral poisons, the extensive fatty degeneration of the myofibrils occurring in fatal cases of acute phosphorus intoxication is well known.

Cor pulmonale and right heart failure are prominent features of *berylliosis* Pulmonary granulomatosis and fibrosis, and obliterating endarteritis are largely responsible for the cardiac changes in this condition.

Alkaloids and glucosides comprise a number of complex organic compounds, many of which are used therapeutically. In excessive doses they may induce toxic effects, which are revealed by diversified physiologic disturbances and structural alterations. Early focal myocardial necrosis, inflammatory-cell infiltration, and late connective-tissue proliferation, were shown by La Due and by Dearing et al. in animals given large doses of digitalis.

The possibility that *drug hypersensitivity* may result in myocardial changes has been suggested by several investigators, but work in this area has developed particularly since the advent of sulfonamides Considerable evidence has been gathered in favor of the contention that myocardial damage may result from the administration of sulfonamides to sensitive individuals Simon has succinctly summarized the pathological characteristics of the lesion which consist mainly of necrotizing arteritis, necrosis of the myofibrils, and exudative reaction (including eosinophilia), which may progress to the formation of mature granu-

a result of accidents such as falls from a height or burial under an avalanche of debris. It is postulated that this type of accident greatly increases the diastolic pressure of the aortic column of blood against the closed aortic valve This concept is supported by the fact that usually the *tears* are only partial, because, as soon as the rupture occurs, the pressure is relieved The passing of a stiff catheter through the valve against the flow of blood will rupture or injure the cusp in a high percentage of instances.

The anatomy of the mitral valve is different with its large, broad, thick cusps supported by the chordae tendineae that act as a protection from rupture. It is postulated that overextension of the cusps during compression of the heart results in rupture of the chordae tendineae and papillary muscles rather than of the valve leaflets Small incomplete tears and areas of hemorrhage may occur on the atrial side The latter type of lesion is also found on the pulmonic and tricuspid valves, but rupture is rare and, when it occurs, it is invariably associated with other severe cardiac injuries The question of *infectious endocarditis* following cardiac trauma is controversial and, in the majority of the cases reported, the lapse of time was inconsistent with cause and effect

Rosenbach, Orth, Wyssokowitsch, and Weichselbaum were the first to experimentally produce traumatic valvular endocarditis by injecting bacteria into the circulation following injury to a valve It is possible, as suggested by Litten and others, that the thrombus formation at the site of small endocardial injuries may become a focus for a subsequent infectious endocardial process and the accumulation of thrombotic vegetations. It is unlikely that an uncomplicated injury to a valve will, in the healing process, create sufficient thickening to produce a stenosis However, if complicated by infection (especially one of rheumatic origin), the thickening, contraction, and adhesions of the cusp can produce stenosis. There is a question as to just how bacteria enter the heart following nonpenetrating injuries while other organs, such as the spleen, when contused or even ruptured, rarely develop infection Frequently, there is some other injury to the body which could provide a point of entry Subacute bacterial endocarditis can be superimposed upon a traumatic lesion.

Cardiac Rupture. Rupture due to bursting may produce a sharp, smooth, clean-cut wound, larger on the outside of the myocardium than on the inside, and usually it does not approximate the place where the force was applied As a rule, these lesions are lengthwise in the ventricles Rupture can occur within a few days after myocardial contusion, when the area is undergoing necrosis, or still later, when the healing process has produced thinning of the myocardial wall and subsequently a cardiac aneurysm. Ruptures frequently occur at the base or margin of the atria, base of the tricuspid valve, and at the junction of the large vessels, especially the veins, due to violent displacement of the heart. Occasionally, the heart is torn completely loose, and has been found free in the pleural cavity

Injury to the Great Vessels. Injury to the great vessels is frequently caused by violent displacement of the heart in the chest, and usually is a complication of cardiac trauma. Crynes and Hunter found that lacerations of the inferior vena cava were frequently accompanied by fractures of the lower ribs on the right side, and Stephens (1922) reported a case with a fracture of the sternum, and a tear of the superior vena cava These injuries are not as frequent as those that affect the aorta. Ruptures and tears with aneurysmic formation due to displacement most frequently occur at the top of the arch of the aorta This can be explained on an anatomical basis, as postulated by Jaffe and Sternberg (1919) and by Shennan (1929). The ligamentum arteriosum joins the aorta near the root of the left lung and is anchored to the vertebral column by connective tissue The aortic attachment acts as a fixed point, and the resulting hinge-like action is responsible for the localized point of injury. The tears are transverse. Also, the anterior wall of the aorta is not as thick as the posterior, and the latter may be crushed against the vertebral column as the result of a blunt impact as well as of direct violence to the chest.

A sudden and violent compression of the systemic arteries, sufficient to markedly distend the aorta at the time of cardiac systole, can cause the intima to rupture and blood to extravasate, gradually distending the elastic coat and occluding the vasa vasorum with resulting

the large arteries, and vary in size from small petechiae to large bruised areas. The infrequency with which uncomplicated hemorrhages of the pericardium are found at necropsy is due to their tendency to absorb completely. Reiss et al. described a case which showed areas of epicardial and pericardial hemorrhage, with clinical evidence of pericardial damage that was probably due to the frequent intermittent use of an *electric pacemaker* for controlling complete heart block with Stokes-Adams syndrome.

In severe injuries caused by being crushed or falling from a high place, the force is transmitted from within, rupturing the myocardium first, and then the visceral pericardium. During violent compression, the great vessels are shut off, putting the fluid mass under great tension which produces rupture through the expanding internal pressure. Tears at the roots of the great vessels appear to be due to violent displacement of the heart. *Infectious pericarditis, pneumopericardium, hemopericardium,* and *herniation of the heart* due to pericardial retraction, are the most frequent complications of pericardial rupture. The small lacerations, hemorrhages, and contusions of the pericardium frequently heal without adhesions. However, when adhesions do occur, they may range from a single fibrous stand to an adhesive pericarditis. Constriction of the superior vena cava, its branches, the trachea, the bronchi, the esophagus, or even fixation of the heart, may result from adhesions caused by hemorrhage (with or without infection) into the posterior-mediastinal space.

Myocardial Injury. The early myocardial lesions of contusion are characterized by hemorrhage into the interspaces between the muscle fibers; these appear to crowd the fibers aside. There is also fragmentation and tearing of the muscle fibers. The smaller hemorrhages are usually found in subepicardial or subendocardial areas. However, these areas may only be the apex of a large triangular area of myocardial contusion. Occasionally, the papillary muscles are involved and sometimes torn. The pathological changes develop in the following manner: first the muscle fibers lose their transverse striations, then become swollen with granular or lumpy protoplasm, and are finally surrounded by a wall of granules and polymorphonuclear leucocytes. This lesion is usually the result of severe contusion, deeply situated in the myocardium and requiring many serial sections to reveal its presence. Grossly, these lesions are more obvious after fixation.

In the older lesions, there is (1) displacement (or replacement) of the myocardial fibers by fibrous-tissue scar formation; (2) muscle-fiber destruction caused by anemic necrosis with absorption, and (3) connective-tissue replacement. These changes frequently lead to aneurysm formation due to myocardial thinning. The lesions are very similar to those of myocardial infarction. Moritz and Atkins reported the similarity. When there is a question of possible or probable trauma, the burden of proof for myocardial infarction rests upon finding a coronary artery occlusion. The older lesions are even more difficult to differentiate because the scars are frequently identical. Hemosiderin and brown atrophy have been observed more frequently in myocardial contusion, but their absence does not exclude trauma.

Endocardial Injuries. These lesions vary from small petechial hemorrhages to large areas of bruising. The larger hemorrhages frequently have the appearance of a hematoma and occasionally the underlying myocardium is necrotic. Frequently, they are *tears in the endocardium* with or without involvement of the myocardium, and they usually heal by scar-tissue formation.

Traumatic rupture of either normal or diseased valves may occur. However, great care should be taken to differentiate the latter from spontaneous rupture. The tears that do not heal result in fragmentation of the free edge of the cusp with occasional severing of the chorda tendinea. Tears or hemorrhage along the base or commissure of the leaflet heal with the formation of scar tissue. The fragmented parts of the valve cusps may grow together, smoothing the rough edges, or become attached to the wall of the heart. Complete healing with obliteration of the opening is rarely accomplished. This process thickens the cusp, thus producing some stenosis with insufficiency. Reubold believes that valvular stenosis and insufficiency can be produced by distortion of the valve ring due to the healing process following hemorrhage or contusion. Most valve ruptures occur on the left side of the heart. The aortic valve is most frequently injured as

with chest pain and at first a slow heart rate but, as *tamponade* develops, the pulse becomes rapid and weak. The heart sounds are muffled and distant as the arterial pressure falls, and the venous pressure is increased with engorgement and distention of the neck veins. As the circulation fails, a marked *pallor with cyanosis* develops, and the patient finally becomes unconscious. Percussion will show an increase in the area of cardiac dullness and the diagnosis can finally be established by tapping the pericardial sac and withdrawing blood One would expect the symptoms and findings of myocardial contusion and those of myocardial infarction with myomalacia to be similar, if not identical, because of the physiological reaction to the pathological process. The differential diagnosis is extremely difficult and occasionally impossible The possibility should be considered that a coincidental coronary-artery occlusion may occur within a relatively short time after an accident However, too many cases of chest injury have been diagnosed as coronary-artery occlusion with complete disregard of a possible myocardial contusion It is also possible that a myocardial contusion can befall a heart that is already damaged by some other type of disease.

Cardiac arrhythmias appear to be influenced by the location of the injury. *Premature contractions* are the most frequent and they originate from any part of the heart. *Atrial fibrillation and flutter, AV or SA block* may occur, and are diagnosed by their characteristic signs, symptoms, and electrocardiographic changes. *Atrial or nodal tachycardia* occasionally occurs, and is not considered a serious complication. However, *ventricular tachycardia, ventricular fibrillation*, and *nodal rhythm*, which occur with cardiac rupture and severe myocardial contusion, can be the cause of *sudden death* within a few minutes after injury Almost every arrhythmia has been produced experimentally These include atrial fibrillation, atrial flutter, premature contractions, *nodal rhythm*, *SA block*, complete AV block, intraventricular block, ventricular tachycardia, ventricular fibrillation, alternating right and left bundle branch block, and various types of nodal rhythm with atrial paralysis.

The electrocardiographic changes are similar, if not identical, to those in coronary occlusion, however, the unipolar leads are useful in locating the position of the injury and identifying traumatic pericarditis. As in myocardial infarction, these changes frequently do not occur until after 24 to 48 hr have elapsed, and therefore serial tracings should be taken This is important because, in myocardial contusion, the electrocardiogram tends to return to normal, or toward the pretraumatic electrocardiogram, in a much shorter time than in myocardial infarction

Cyanosis that cannot be attributed to lung injury is an indication for angiocardiography or cardiac catheterization, since these procedures will identify atrial or ventricular septal ruptures and are helpful in diagnosing acquired left-to-right shunts

If, shortly after an injury, roentgenographic examination of the chest reveals increased density and widening of the upper part of the posterior mediastinal space, examination should be repeated weekly because these changes are evidence of contusion, hemorrhage, and partial rupture of the great vessels. The accepted signs of *aortic aneurysm* may be present from 1 to 4 months. However, pulsation of the shadow is often not seen because of thrombus formation

MANAGEMENT AND TREATMENT

Patients with severe symptoms of cardiac trauma, i.e., dyspnea, orthopnea, or cyanosis should receive oxygen continuously for 4 to 7 days A narcotic or sedative may be necessary to relieve the pain and anxiety. *Pulmonary edema* may develop, especially if there is an associated contusion of the lungs, and this should be treated in the usual manner. However, venesection is not recommended unless it has been definitely proved that the attack is due to heart failure[1] *Digitalis* is indicated when there are signs of congestive heart failure or atrial fibrillation with a rapid ventricular rate, but it will not control the sinus tachycardia which is so frequently present The routine administration of digitalis is not indicated, because the frequent ectopic rhythms suggest that the area of myocardial damage has an increased excitability In the cases of ectopic rhythm established at the time of injury, an immediate attempt should be made

[1] For the mechanism and therapy of pulmonary edema, see Part 18, Chaps 12 to 14 *Editor.*

fusiform or saccular aneurysm formations. *Aneurysms of the aorta* due to peripheral compression (e g., when the patient has been covered by debris and forced into a jackknife position) are usually located in the abdominal portion. External chest injuries that produce bruising, with hemorrhage into the wall of the aorta and tears of the intima, rarely result in a dissecting aneurysm. A traumatic aneurysm is not a true aneurysm but rather a hematoma A saccular aneurysm can form later as a result of the stretching of the scar tissue.

SYMPTOMS, PHYSICAL MANIFESTATIONS, AND DIAGNOSIS

After considering the pathogenesis of traumatic lesions, it is obvious that they will produce similar, if not identical, symptoms and physical findings to lesions produced by other causes. The patient's history is all-important, and a correct appraisal must be made of the cardiac condition before, at the time of, and immediately after, the trauma. With *rupture or tears of the pericardial sac,* there occasionally is a *double, loud and soft, systolic murmur,* with a sharp interruption. This was described by Morel-Lavallée as similar to the sound of water striking the blade of a wheel (water-wheel murmur). The sound may also resemble that produced by blowing into an empty bottle. *Pericardial contusion and hemorrhage* will produce a *soft to rough systolic murmur,* and a *friction rub* may replace the murmur at any time These murmurs may disappear for a few pulsations or upon change of body position.

Severe *precordial pain* developing immediately, or at least within 6 to 12 hr, is the most persistent symptom *Dyspnea* and *orthopnea* occasionally occur, and there may be *precordial distress* on breathing. *Tenderness over the precordium* and *palpitation* are symptoms which persist for some time When the murmur is due to a ruptured valve, it occurs immediately, is constant, and is associated with a characteristic sign of valvular insufficiency Rupture of the chordae tendineae causes a *vibrant murmur,* like the sound of a jew's-harp. It will frequently disappear when the broken chordae become entangled or adhere to the sides of the cardiac cavity.

The cardinal symptom of *myocardial contusion is immediate, excruciating pain* located in the substernal or precordial area and radiating (usually) to the left shoulder and left arm. It may also be referred to both shoulders or to the sides of the neck. The pain is identical with that experienced in coronary insufficiency or coronary occlusion. When the patient is unconscious, or the physician's attention is distracted because of fractures of the ribs or severe injuries to other parts of the body, the substernal pain is not the cardinal symptom and may be overlooked. Occasionally, it occurs after a latent period of from a few days to 2 weeks A *silent myocardial contusion* can occur, as well as a *silent myocardial infarction.* Necropsies have revealed many symptomless myocardial contusions caused by minor injuries. The *serum transaminase* level is elevated as it is in myocardial infarction The symptoms should be differentiated from those produced by contusion and fracture of the thoracic cage. Later, the pain of myocardial contusion can be brought on by exertion, and, like the coronary type of pain, it is referred to the left arm and relieved by rest.

In about 25 per cent of the cases, the appearance of symptoms is delayed up to a month, but the signs of myocardial weakness, revealed by venous congestion and nocturnal dyspnea, usually develop after a short latent period. The most common findings in all cases of myocardial contusion are *tachycardia, palpitation,* and *arrhythmia.* The arrhythmias present their own characteristic signs and symptoms. Frequently, auscultation reveals nothing unusual However, should the heart sounds seem distant at any time, a roentgenogram, electrocardiogram, or even a pericardial tap should be made immediately to confirm the possibility of a *hemopericardium.* In all cases, a roentgenographic examination should be made as soon as possible, not only of the heart, but also of the anterior and posterior mediastinal spaces. The examination will reveal whether or not there has been *hemorrhage about the great vessels.* If it is done early, the films can be compared with subsequent ones, should a question arise in regard to cardiac aneurysm or hemopericardium A roentgen kymogram or electrokymogram offers, not only a means of diagnosis, but considerable assistance in locating the area of contusion in the heart.

Cardiac rupture produces sudden collapse

ture of the left ventricle. Death, however, depends upon the size and the speed of the hemorrhage.

The small pericardial and subpericardial lesions heal uneventfully, but the more extensive or obliterating types may interfere with cardiac output, thus hastening heart failure *Cardiac fixation* due to adhesions frequently results in permanent disability. *Cardiac tamponade* causes sudden death or rapidly progressing failure The heart can also be embarrassed by clot formation in the pericardial sac from even a small wound. Obliteration of the sac by adhesions may result in calcification and an *armored heart* (constrictive pericarditis) A rupture of the pericardial sac which allows blood to escape defeats tamponade and delays death. Pericardial injuries heal more rapidly than those of the endocardium. The prognosis for partial or even complete recovery in cases of uncomplicated mild and moderate cardiac injury is good Uncomplicated hemorrhages have the best prognosis, certainly better than that of contusion or rupture caused by nonpenetrating injuries which involve more than one chamber.

The juvenile heart has a more favorable prognosis because it is smaller, and children are less likely to be exposed to the bursting type of injury. Anderson reduced the possibilities following myocardial contusion to (1) complete recovery, (2) reduced cardiac capacity, (3) pain on effort, (4) congestive failure, or (5) cardiac rupture.

PENETRATING WOUNDS AND FOREIGN BODIES

Historical Background and Mode of Injury. The wound at present is usually produced by a knife, ice pick, bullet, or fragments of bone; earlier causative instruments were spears and arrows. There are many important factors to be considered, e g, (1) the character of the knife blade (was it sharp or dull, blunt-tipped or pointed, round or flat, thin and narrow, or broad and thick); (2) the caliber of the gun and character of the projectile (single or multiple, lead or steel, soft-nosed or hard-jacketed), (3) the distance traveled by the lethal object and the angle at which it entered the body

A penetrating wound of the heart may be caused by a bony fragment, fractured rib, or the sternum, in these wounds there may be no penetration of the thorax It is also possible to have a penetrating wound of the heart due to a foreign body, such as a needle entering from the esophagus or bronchial tree.

Elsberg believed that wounds which were inflicted during systole bled more strongly than those incurred during diastole. He explained that wounds cut during systole become larger in diastolic relaxation, while those cut in diastole become smaller during systole. Harvey mentioned the case of a stag in which a bullet was found lodged within the heart Callender (1871) removed a needle from the heart; this is the first case recorded where any surgical treatment was attempted. Decker reviewed 109 cases of foreign bodies in the heart; these had been reported between 1900 and 1939 The foreign bodies reported form a miscellaneous collection which includes such items as needles, safety pins, nails, iron pegs, hairpins, bullets, shrapnel fragments, skewers, aluminum pipestems, splinters, toothpicks, bone, teeth, and dentures. Iverhardt reported 22 cases of unsuspected needles in the heart.

Pathologic Changes. Borellus (1682) described a lesion of the cardiac muscle with hemopericardium which resulted from a shot which did not perforate the pericardium. Elkin (1936) reported that 2 per cent of all penetrating wounds of the chest injured the heart. However, he commented that, if those who died before reaching the hospital were counted, the percentage would probably be much higher. The right ventricle is most frequently wounded because of its anterior position. Small puncture wounds of the heart at first show hemorrhage of the epicardium and myocardium with clot formation. Within 5 days, the clot is covered by a layer of cells, shortly afterwards organization of the clot is completed and the thrombus is covered by epicardium.

In the myocardium, there is effusion of blood in the vicinity of the wound, and the muscle fibers are pushed apart, this causes degeneration. Within the first 24 hr the gaps between the edges of the wound are infiltrated with fibrin and leucocytes There is a marked accumulation of leucocytes between the muscle fibers, and from the second to the fourth day granulation tissue forms Shortly afterwards, there is connective tissue in the scar formation

to reestablish sinus rhythm. Frequently, spontaneous reversion occurs, but atrial fibrillation has a tendency to recur and to become permanent. If, after the injury, the heart still has normal sinus rhythm, it is advisable to administer small doses of quinidine sulfate every 3 to 6 hr for the first few days, for the purpose of preventing atrial fibrillation, flutter, ventricular tachycardia, or ventricular fibrillation.

The pain of myocardial contusion is reduced in severity by the administration of *nitrates* and *papaverine hydrochloride,* but the discomfort does not completely disappear. The effects of these drugs are similar to those seen in treating myocardial infarction and, in general, the treatment should be basically the same. The period of bed rest should be from 2 to 6 weeks, depending upon the classification of the patient as a good or poor risk. However, this period is frequently prolonged by injury to other parts of the body The complication of *shock* due to cardiac injury should be treated like that which follows myocardial infarction. The associated traumas require their special surgical or medical treatments but, above all, great care should be taken during convalescence to prevent the development of a *cardiac neurosis.*

Reim stated that, although about 30 per cent of all patients with serious cardiac injuries came to the hospital unconscious and often apparently moribund, one should not question the possibility of their survival. Regardless of the apparent hopelessness of cases of tears and ruptures, surgery should be undertaken. The advice of Beck is sound, that repeated tapping of the pericardial sac should be performed, not only to confirm the diagnosis, but also to relieve cardiac tamponade until surgical intervention is possible In shock and collapse, the heart should not be massaged, but only lightly stimulated, because the areas of injury may be extended by fresh hemorrhages. Cardiac massage, although sometimes successful, may be only temporarily so, and can produce myocardial contusions. Therefore, it is safer to use instrument percussion, electrical stimulation, or intracardiac injection. Fractures of the thoracic bony cage with deformities that decrease the anteroposterior diameter of the chest should be corrected so that they do not cause compression or displacement of the heart. Posterior mediastinal hemorrhage occasionally requires surgical intervention to prevent adhesions with cardiac fixation. Steinberg states ". . . that the mere presence of an aneurysm is not an indication for operation Surgery should be restricted to patients who require relief of symptoms or have evidence of enlargement of an aneurysm."

PROGNOSIS

While *valvular rupture* is not associated with sudden death or usually fatal, it must nevertheless be considered as a serious type of injury. *Traumatic insufficiency of a valve* produces a sudden strain on the chamber behind the valve, whereas, in insufficiency produced by disease, the strain is produced gradually. This sudden strain does not allow sufficient time for hypertrophy of the myocardium, and failure follows rather rapidly. The duration of life is, therefore, shorter in rupture of the aortic and mitral valves. Fatal *emboli* may occur, with or without sudden death, from a focus of fibrin or small blood clots on the torn valve leaflets. The healing process in minor injuries to the valve cusps, such as hemorrhage, may later produce an incompetent valve. However, the majority will recover with only slight, if any, damage. The prognosis becomes grave if these valvular injuries are complicated by an inflammation of the endocardium, myocardium, or pericardium.

In *myocardial contusion,* the gravity of the prognosis depends upon the number and extent of the lesions. There is, however, a definite tendency toward rapid healing, especially if the lesions do not extend too deeply into the heart wall. After the more extensive lesions have healed, myocardial insufficiency frequently becomes apparent. Sudden death from *cardiac rupture* does not always occur, and there are numerous cases reported of patients who have lived for 2 or 3 days. Contusions involving the intrinsic nerve mechanism of the heart frequently produce permanent or immediately fatal arrhythmias. *Tears of the cardiac septa* may heal but, if the bundle of His is involved, the work capacity of the heart is diminished. *Rupture of the atrial wall* is most serious, because the thinness of this wall does not allow the opening to be closed with muscle contraction. It has long been observed that the lowest percentage of sudden death is in rup-

ture of the left ventricle. Death, however, depends upon the size and the speed of the hemorrhage

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and usually within 1 to 2 weeks there is no visible trace of the puncture. Punctures of the left ventricle are likely to bleed slightly, whereas those of the atria bleed profusely. The fibrous-tissue healing of the myocardium may be firm or the wall may become thin with formation of an aneurysm. The effusion of blood into the pericardial sac is absorbed rather rapidly, especially if there is no infection to cause either partial or complete adhesive pericarditis. Occasionally, a wound of the ventricles will not completely penetrate the wall and injure the endocardium. However, this does not occur in the atria.

Stab wounds usually have a clean-cut edge, whereas those made by projectiles are frequently jagged and irregular, and have more than one opening. The wound may involve the valves, capillary muscles, chordae tendineae, and the interventricular septum. Valvular trauma may be due to effusion of blood from a nearby wound or dilatation of the valve ring by an aneurysm of the heart. Occasionally, a foreign body will be caught in a valve, a papillary muscle, or chorda. Wounds of the pleura and lungs frequently accompany those of the heart.

The intentional penetrating wounds inflicted during cardiac surgery may produce the same signs, symptoms, pathological changes, and complications as accidental wounds. Contusion of the myocardium or papillary muscles, and rupture of the chordae tendineae have resulted from too vigorous manipulation by surgeons. In these penetrating wounds, the primary cause of death is usually shock, fatal arrhythmias, or hemorrhage. The secondary cause of death is carditis, endocarditis, pericarditis, pneumonitis, pleuritis, embolism, abscess, aneurysm, and exhaustion. *Pericarditis* is probably the most frequent complication of any degree or type of cardiac injury. *Air and other emboli* occasionally cause death, and should be feared in all cases in which the injury or surgery extends into the cardiac cavities. There may be *abscess* formation in the heart wall, pericardial sac, mediastinum, or pleural spaces. *Aneurysms* form in the scar tissue at the site of the injury. Fragments of a fractured sternum or rib occasionally tear the pericardium. This type of injury may be assumed when the tear exactly corresponds to the fracture of the bony cage.

Piercing injuries to the pericardial portion of the thoracic aorta usually lead rapidly to death, because there is no surrounding structure to limit the loss of blood. The short intrapericardial part of the aorta is only occasionally injured because of its position behind the sternum.

It is very difficult to determine whether the transportation of a projectile embolus is ante- or post-mortem. Evidence of fresh dislocation and movement does not necessarily imply that the motion definitely existed before death. Intramuscular movement of a foreign body may be influenced by the position of the body, respiration, muscular contractions, force of gravity, and, to some extent the blood flow, or some combination of these forces. The point of entry of the foreign body is most frequently in the chest; however, it may enter through the esophagus, bronchi, or blood stream via a pulmonary vein, or one of the venae cavae, and migrate to the heart cavity.

Foreign bodies that reach the cavities of the heart may migrate as *projectile embolisms* into the arterial system, or they may become attached to the heart wall by clot formation with fibrosis and calcification. Occasionally a bullet will plug a wound in the heart wall and be surrounded by clot formation and the inflammatory reaction of the endocardium and pericardium. If the foreign body enters from the esophagus or the bronchi, there is invariably an *adhesive pericarditis*. Abscess formation, of course, is always possible at the site of the foreign body, but usually it is encysted or encapsulated by fibrous tissue. The fibrosis surrounding a bullet may resemble a fibroma and become calcified.

Complications. Of the later complications of wounds to the heart, the most frequent are adhesion, obliteration, and calcification of the pericardium. *Mediastinopericarditis* has occurred in a few reported cases. Various disturbances of rhythm such as atrial fibrillation and complete heart block have occurred. *Cardiac aneurysm* may be an occasional complication occurring at the site of the foreign body removal. *Pleural effusion* is almost inevitably a complication, and requires repeated aspiration and even rib resection if an infection develops and cannot be controlled by antibiotics.

Signs and Symptoms. Penetrating wounds of the heart are seldom dry, but are accompanied by profuse hemorrhage which may not be visi-

ble outside of the body. Penetrating wounds of the aorta, venae cavae, or pulmonary vessels are invariably and rapidly fatal.

The diagnosis of injury to the pericardium should not necessarily be difficult, but it is safer to explore the pericardium than to take the chance of an undiagnosed hemorrhage with cardiac tamponade. One should not be misled by the statement that, following the injury, the victim continued great activity for a short time. A significant sign is a wound in the precordial region, but it may be somewhat distant, in which case there is copious hemorrhage Loss of consciousness may be the result of asystole due to hemopericardium or of cerebral anemia resulting from the marked hemorrhage. Muscular twitchings and restlessness may advance to convulsions Frequently, there is a symptom-free period of from 5 to 10 min following the injury, and usually, by this time, *there is a cessation of the bleeding from the* external wound The author would advise against probing, but it is possible in this way to determine whether the heart has been injured (the instrument pulsates) The external hemorrhage may be small, excessive, pulsating, or oozing, or there may be a steady flow. Whether it is arterial or venous blood cannot, as a rule, be determined If the hemorrhage is pulsating, it may have originated in the heart, internal mammary or intercostal artery, or one of the pulmonary vessels, however, absence of pulsation does not eliminate the possibility that these vessels may be injured

When a penetrating wound of the chest involves the pericardium, heart, or great vessels, there is invariably severe *shock* with unconsciousness, cold perspiration, increased respiration, widely dilated pupils, and all the other classical signs The facial expression indicates great distress and anxiety. Frequently, there are signs of air hunger, such as sighing, yawning, and gasping for breath. The pulse is very weak and frequently imperceptible If the blood escapes into the pericardial sac, the anemia is not as pronounced as when it pours into the thorax *Cyanosis*, when it occurs, does so in various degrees depending upon the size of the wound, the amount of hemorrhage, and the extent of its interference with respiration. The venous pressure is frequently increased, and the neck veins are engorged, with extreme dyspnea and marked anxiety. There is a marked drop in arterial blood pressure, and the latter may become unobtainable *Delirium*, taking on a violent form, may follow wounds to the heart, it is probably due to prolonged cerebral anemia resulting from extensive hemorrhage and low blood pressure.

The presence of *pneumothorax* may prevent satisfactory examination of the chest; however, a large area of cardiac dullness would suggest the possibility of hemopericardium. The so-called *spinning-wheel* or *water-wheel murmur* is rarely heard The most precise information is obtained by roentgenographic examination, which reveals the size and immobility of the cardiac shadow and the presence of hemopericardium. It should be remembered, however, that death can also occur from a rapidly developing tamponade which originated from an amount of blood too small to change the contour of the cardiac silhouette. The *electrocardiogram* is frequently normal for several hours following the injury. *Electrokymography* should be of some assistance. The diagnosis of cardiac tamponade is practically certain if there is a rising or high venous pressure and a falling or low arterial pressure together with an absence of cardiac pulsations on fluoroscopic examination Abnormal ballistocardiographic tracings should be somewhat of an aid If the diagnosis is otherwise impossible, aspiration should be performed. Roentgenographic examination will also reveal the presence of cardiac aneurysm or constrictive pericarditis.

Following the healing of penetrating wounds, there are frequent attacks of *precordial pain*. Substernal pain occurs, especially if a coronary vessel was involved by the wound or was tied in the course of the operative procedure. The presence of a foreign body in the heart is frequently discovered only at autopsy. There may be a deep-seated sensation of weight, heaviness, or oppression. When there is inflammation of the pericardium, the pain is acute and cutting in character It may be continuous or periodic, brought on or intensified by exertion and change of position, such as lying down Punctures of the heart cause very little, if any, pain. *Dyspnea*, another frequent symptom, is usually present only on exertion unless heart failure occurs. There are frequent attacks of palpitation, tachycardia, weakness, fatigue, and syncope, with occasional cyanosis.

Every type of *cardiac arrhythmia* may occur

depending upon the site of injury, location of foreign body, and mode and type of reparative or operative procedure. Premature contractions are probably the most frequent arrhythmia. Serial electrocardiograms may show the various changes that are seen in coronary-artery occlusion with myocardial infarction. These changes may be transient or remain permanent. Frequently, the electrocardiogram shows only myocardial change. There may be abnormalities in all leads, involving the various waves of the electrocardiogram and there may be evidence of delay in conduction. The changes may be consistent with, or similar to, those seen in pericarditis, and they frequently suggest an acute pericarditis rather than a lesion of the myocardium. The electrocardiographic picture in acute myocardial injury depends upon the location of the injury. It may serve a purpose in determining the presence of a wound in the precordial region and whether or not the heart is involved, and will give information as to whether or not a coronary artery has been severed, and also the location of the myocardial damage.

Foreign bodies frequently produce morbid symptoms only when the object changes its position due to movement of the heart. Needles, thorns, and other sharp objects which penetrate from the esophagus may remain without symptoms or damage because their progress through the tissue of the heart is slow and an inflammatory process closes the wound behind the object

Small objects, or those that are not of opaque material, can seldom be seen on roentgenographic examination. In order to ascertain whether a foreign body is intracardiac, its shadow should be seen under the fluoroscope to be within the cardiac shadow in the anteroposterior position, both oblique positions, and when the body is flexed from right to left at the waist. Its movement should also be synchronous with that of the heart shadow, not the diaphragm. If the foreign body is free in the heart cavity, it may occasionally be seen to whirl around in an irregular motion. The history and symptoms may suggest a foreign body but the diagnosis is only definitely established [illegible] and [illegible] to [illegible] ign

body in or about the heart. It is remarkable how the movements of the heart may be communicated to a foreign body.

In some patients symptoms occur only when an attempt is made to resume an active normal life. The difference in the consequences depends on the position of the foreign body in the heart. It must always be remembered that the cardiac symptoms may be neurotic in origin.

Treatment. Matas (1921) wrote "The road to the heart is only 2 or 3 cm in length in a direct line, but it has taken surgery nearly 2,400 years to travel it."

Large doses of *antibiotics* should be given immediately, and even injected directly into the pericardial sac in an aggressive attempt to prevent infectious pericarditis However, if infection develops, complete drainage is necessary, and, if at all possible, the patient should bend forward in a position he would assume if he were standing on his head, since this maneuver will cause the ventricle to move forward and the cul-de-sac of Haller will be open. It is safer to do an *exploratory pericardiotomy* than to run the chance of death from cardiac tamponade or hemorrhage. It is doubtful whether the surgeon should ever place his finger in a wound of the myocardium because the muscle is extremely friable and the wound frequently is torn and enlarged. There should be no attempt to separate the pericardial visceral layers in pericarditis; it is preferable to remove a large portion of the pericardium.

Should *ventricular standstill* or ventricular fibrillation occur, immediate gentle massage should be started and a *defibrillator* used Gentle massage should be at the rate of about 40 to 50 contractions per minute. Ventricular fibrillation may be produced by any type of manipulation of the heart, even the placing of a suture, but it can frequently be prevented by the use of *procaine solution* administered both intravenously and topically to the surface of the heart. When ventricular fibrillation is already established, intermittent, regular manual compression may break the arrhythmia Since atrial fibrillation occasionally occurs during the operative procedure, it is wise to administer *Pronestyl* or *quinidine* as a preventative of both the atrial and the ventricular arrhythmias.

In the case of old wounds containing foreign bodies, in which the patient has the appearance of perfect health with no functional disturbance, it is important to consider the psychic elements before definite statements are made. Frequent *neurotic manifestations* develop, depending upon the attitude of the patient toward the knowledge that he harbors a foreign body in his heart. *Psychotherapy* should be directed not only to the patient but also to overanxious relatives and friends, and against ill-advised surgical intervention The question of surgical removal should be weighed very seriously since accumulated experience has shown that most foreign bodies probably become safely encysted and will do no harm. Turner (1941) states, "The fear of infrequent late complications should not be made an excuse for intervention when the patient is symptom-free, and it would be a good rule to leave the foreign body alone unless the heart *continues to rebel* against its presence." If definite symptoms develop or persist, then intervention, of course, should be considered.

Foreign bodies located in the ventricles or near the apex present a much easier surgical problem than those in the atria. If a foreign body in the pericardium is causing symptoms, it can be easily removed with little risk Most surgeons advise the removal of long, thin objects such as needles or wires, and loose objects within the heart cavity; the former because, if they are removed early, usually do not give rise to marked anatomical changes, the latter because of the dangers of pulmonary or systemic embolus Large foreign bodies in the pericardium should probably be removed as early as is practicable This, however, does not pertain to the intramural type Symptoms engendered by foreign bodies usually disappear with their removal

Many penetrating and nonpenetrating injuries caused by projectiles, bomb fragments, and automobile accidents, could have been avoided by the use of suitable protective devices such as plastic armor, and, in the case

... penetrating wounds alone were instantly mortal, especially those of the left ventricle

The prognosis of a penetrating wound is always serious, but many cases are amenable to immediate repair with subsequent recovery. The time of death following a heart wound depends upon the size, and whether the hemorrhage is fast, slow, to the surface of the body, or into an enclosed cavity. Wounds of the atria are usually considered more dangerous than those of the ventricles, and those of the right atrium even more dangerous than those of the left The direction of the wound is important. In an oblique wound caused by a shot or a stab, there is a possibility of valve-like closure due to intracardiac pressure. Furthermore, a trabeculum may place itself against the inner surface of the wound Also, the wound might be placed so that, in systole, it lies against the sternum or the ribs, and is thus compressed and partially closed. It is possible also to penetrate and separate a few fibers and not enter the cardiac cavity; the prognosis in such wounds becomes more favorable Penetration of the great vessels is usually followed by death within a few minutes It is possible for a bullet or a foreign body to close the wound and stop the hemorrhage. Occasionally, it happens that complete collapse may have a favorable influence The prognosis is more grave in bullet wounds because they not only frequently cause two cardiac wounds, but also greater tissue destruction. The postoperative prognosis is dependent upon infection, pericarditis, and pneumonia. Makins believes that death is more often due to cardiac standstill than to hemorrhage.

There are numerous reported cases of foreign bodies that have been tolerated in the heart for a long period of time. There have been reports of soldiers returning to active duty, others have engaged in athletic contests and hard labor after foreign body removal The most favorable prognosis is when the foreign body is in the pericardium, next in the ventricle, and most grave when in the atrium or free in the cardiac cavity. Death following removal is most frequently due to infection, occasionally an embolus or hemorrhage, but seldom cardiac failure. Pneumonia with or without infarction, pulmonary embolism, arterial embolism, pericarditis, pleurisy, septicemia, cardiac failure, and cardiac arrest are also frequent causes of death

AIR EMBOLISM

Air embolisms may be either arterial or venous. The latter result from the rapid entrance of relatively large amounts of air into the venous system, and its subsequent lodgment in the right ventricle, causing an air bubble and thus obstructing the outflow. Arterial air embolism occurs when air enters the pulmonary veins and passes into the systemic arteries. A venous air embolism may also cross an atrial or ventricular septal defect and become arterial. Air emboli reaching the lung from a systemic vein do not cross the pulmonary bed to the pulmonary veins and systemic arteries (Curtillet).

Venous air embolism is most frequently a complication of surgical procedures in areas where large systemic veins are encountered, e.g., in the neck and thorax, and in obstetrical or gynecological procedures Diagnostic procedures such as pneumothorax, pneumoperitoneum, peritoneoscopy, perirenal air insufflation, tubal insufflation, cardiac catheterization, urethroscopy, and nasal sinus irrigation are common causes. Criminal abortion, cesarean section, surgical interference for placenta previa, assumption of the knee-chest position in the early puerperium, and prostatic and breast surgery, have all produced air embolisms Transfusions and intravenous infusions are occasional causes.

Clinical manifestations of venous embolism are shock, dyspnea, tachycardia, pallor, and sudden death. A rapid rise of venous pressure causes marked cyanosis and a loud *churning, or water-wheel murmur*, may be heard over the precordium.

Electrocardiographic changes characteristic of myocardial ischemia have been described and are explained by the work of Visscher, who showed coronary blood flow to be dependent on the pressure gradient across the coronary system. The thebesian blood flow is greatly restricted with the rise in pressure inside the right ventricle and, as the aortic pressure falls, the gradient is markedly reduced The air trapped in the right ventricle obstructs the outflow and eventually causes cerebral ischemia. This type of obstruction may also be caused by widespread embolization of the pulmonary arterioles and capillaries.

Once the diagnosis has been established, immediate therapeutic measures are imperative. The patient should be placed in the left lateral position, thus placing the pulmonary outflow tract in the relatively inferior part of the right ventricle and displacing the trapped air upward. Thus outflow is again established and the air is gradually absorbed (Durant et al.). *Narcotics* and *papaverine* should be given for pain and vasospasm. Inhalation of 100 per cent oxygen has been recommended on the basis of experimental studies by Fine and Fishman If these measures are ineffective, an attempt should be made to aspirate the air by inserting a needle into the right ventricle

Arterial air embolism results when air enters a pulmonary vein and passes through to cause ischemia in such vital organs as the brain and heart. Pneumothorax, thoracentesis, and thoracic and open-heart surgery are the procedures most commonly involved. Rapid ascent, either from ocean depths (*caisson disease*) or to high altitudes, is another cause. Catheterization of the left heart has been known to accidentally cause air embolism.

Various *neurological manifestations*, i.e., coma, convulsions, aphasia, hemiparesis, and others may develop, depending on the cerebral vessels involved. Ophthalmoscopic examination may reveal air bubbles in the retinal arteries. The skin of involved areas develops a marbled appearance. A small skin incision over the superior part of the body may demonstrate air bubbling. Electrocardiographic changes typical of myocardial infarction have been described by Durant (1935).

Therapy is unsatisfactory and mostly supportive. Placing the patient in Trendelenburg position during a procedure in which air embolism is a possibility, may avert cerebral embolization Prophylaxis is definitely the best measure

8

Poisoning of the cardiovascular system

FRANKLIN C. MASSEY

Any material which is detrimental to the normal functions of the living organism is called a "poison" Most substances conventionally used *to maintain and reestablish the physiological or normal status of health may, under certain circumstances, be included in this category* Other substances, never intended for human contact or ingestion, often deleteriously affect the integrity of the healthy organism.

POISONS

A number of *poisons* are properly used as *drugs* (digitalis is perhaps the most *common* of these), while certain common chemicals, such as carbon tetrachloride, were never intended *to have* desirable human applications. *Striking exceptions* to such generalizations include potent compounds like strophanthin, eserine, the mustards, and a host of others, *which* have come into use as drugs (in smaller doses) after having been designated as "poisons."

Poisons, or substances which are noxious to the well-being of the human cardiovascular system, may be further classified as exogenous *or* endogenous.

Snake Venom. Cardiovascular abnormalities due to the proteolytic snake venoms are *rare in the* United States and are usually limited to vascular phenomena. *Hemolysis, alteration of blood coagulability,* and *local necrotizing effects* are characteristic lesions *secondary* to venomous snake bites, besides the neurotoxic manifestations. *Multiple, focal, myocardial hemorrhages* undoubtedly contribute to death due to snake venoms, these are *accentuated* at times by the "spreading" activity *and increased* capillary permeability induced by the potent toxin. In effect, myocardosis, pericardosis (due to hemorrhage), *or both, are produced* by the snake venom Remarkably, intracardiac blood remains incoagulable for up to several hours post-mortem in fatal instances.

Because of the paucity of information on *this subject* in cardiovascular literary sources, *two case histories* are presented here. The first was accompanied by minimal, but probably *significant, ECG* aberrations, and is detailed in conventional fashion:

A 38-year-old colored man was *admitted* to a military general hospital for treatment of *a rattle*-snake bite approximately 24 hr old *He was a carni*val worker, and his occupation involved handling snakes The patient was bitten (by a 2½-ft *rattle*snake) *over the dorsum of the left* thumb and in the web space between the thumb and index finger *He quickly incised* the wounds of the fang punctures with a pocket knife and sucked out the blood himself. *Immediately* thereafter, a tourniquet was applied *around the wrist* by one of the other carnival workers. He was taken to a civilian general hospital *about 1 hr later. A* tourniquet was reapplied at that hospital *and* the patient was given 10 mg of morphine. He *was then* transferred to a county hospital were he received 15 ml of snake antivenin, sedation, *and* Neohetramine in three doses of 100 mg each. His left arm was packed in ice from the finger tips to the axilla A urinalysis

was normal. The patient stated that, since his accident, he had suffered three chills and felt feverish following each chill He also felt nauseated, and had vomited three times.

Physical Examination. On admission to the military general hospital, examination revealed a well-developed, well-nourished colored man who did not appear acutely ill, but who was drowsy and lethargic. The whole left upper extremity, from the finger tips to the axilla, was diffusely swollen, red, tense, and tender. One fang mark was seen over the proximal dorsum of the left thumb, and another in the web space between the thumb and index finger. Both punctures had been cut crosswise by incisions approximately one-fourth inch in length. There was no drainage from these incisions. Blood pressure was 108/80, pulse 84 respiration 20, and temperature 98.6°.

Laboratory Data. Laboratory findings were as follows. hematocrit, 55, leucocytes, 16,700 with 82 per cent polymorphonuclear cells; icteric index, normal, urinalysis normal, except for microscopic examination of the sediment which revealed rare red cells, occasional white cells, and rare granular and hyaline casts. Urinary urobilinogen was normal. The electrocardiogram was abnormal (Fig 16-8).

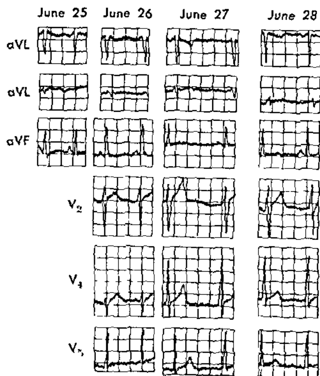


Fig. 16-8. Electrocardiogram of 38-year-old Negro male patient, victim of rattlesnake bite Whether the T-wave variations displayed in these selected electrocardiographic leads have direct myocardiopathologic significance cannot be established unequivocally, but the serial study certainly has merit. (Note especially leads aVF, V_2, V_4, and V_5)

Treatment. The patient was given a booster shot of tetanus toxoid and 1,500 units of tetanus antitoxin. Massive hot wet dressings were applied from the finger tips to the axilla of the left arm The left arm was elevated. Penicillin (50,000 units) was given every 3 hr After 24 hr, there was no essential change. The patient was still nauseated and had vomited once Physical findings concerning the local wound and the involvement of the left arm were essentially the same, except that the edema of the left upper arm had subsided minimally. The patient had remained afebrile, but there was a palpable massive axillary lymphadenopathy.

The second case history is abstracted from a newspaper. Gruesomely fascinating, the account details the generally recognized pathophysiological alterations, but pitifully indicates the lack of perception of the dire possibilities of major cardiovascular complications, including hemorrhagic phenomena of the pericardium or myocardium. A detailed personal medical diary was kept by the 67-year-old victim, the Curator Emeritus of the Chicago Natural History Museum. He had been bitten during the examination of a small tree snake, a South African boomslang. The doctor, himself, was an internationally recognized snake expert.

His account began with a description of the snake and its examination and a conclusion that it was a boomslang because of its behavior when it bit the victim on the left thumb. The reptile had been taken from Chicago's Lincoln Park Zoo to the museum for positive identification. Dr Schmidt's associates said he made the record with no foreboding that he would die He and others at the examination felt he had *not* gotten a lethal dose from the bite and his associates suggested that he make a record of any symptoms that might develop Since the snake was a young one and in captivity for some time, it was thought erroneously that the venom should have been less voluminous and less toxic; the experts erred to the point where use of an antivenom serum was not even considered After being bitten, Dr. Schmidt wrote. "The punctures bled freely and I sucked them vigorously" He reported, "strong nausea, but without vomiting" during an early evening trip by train to his home in suburban Homewood. The next entry, at about 5 30 P.M., said "Strong chill and shaking, followed by fever of 101.7°F., which did not persist. Bleeding of mucous membranes in the mouth began about 4 30 P.M., apparently from the gums."

Three hours later, Dr. Schmidt wrote, he "ate two pieces of milk toast and went to bed." He slept until shortly after midnight, when he awoke, bleeding from the mouth. He reported a good deal of abdominal pain "Took a glass of water at 4.30 A.M.," the diary read, "followed by violent nausea and vomiting" The last entry was made shortly after 7 00 A.M Dr. Schmidt said he had eaten a good breakfast.

The final entry read. "Slight bleeding is now going on in the bowels Mouth and nose continuing to bleed, not excessively." Unattended by a physician, he went into a coma at 2.00 P.M. and, it was estimated that death occurred at about 3 15 P.M. Electrocardiographic and other specific cardiovascular data, of course, were not available.

From a clinical standpoint, the foregoing studies should provide the reader with unforgettable images of (implied) basic pathological abnormalities of the entire cardiovascular system.

Endogenous Poisons. These are chemicals of biological origin, produced within the human host, either by faulty function of a component organ (azotemia, uremia) or by unfortunate residence within the organism of an "opportunist" parasite. In the latter case, they are called *toxins*

A few poisons are biochemicals which are normally present in the human body but cause toxic reactions under abnormal circumstances (lipids?) or in excessive quantity (porphyrins? insulin?) Anions, cations, trace-elements, histamine, and other body substances, may also be included in this group (*see* Part 2, Chap 29)

CHEMICALS

Because of the infinite number of chemicals to which one's cardiovascular system may be exposed, it is impossible to expound knowledgeably on all such situations. It would seem reasonable, profitable, and valid to reflect upon several of the more common chemicals and one or two rather unusual ones

Inorganic Chemicals. While the cardiologically oriented physician might most readily consider the cardiotoxic effects of the heavy metals, especially *mercury*, he must keep in mind such poisons as the trivalent or pentavalent *arsenic*, which are themselves poisons, as are the soluble compounds of arsenic They are extensively used in medicine, as industrial pigments or insecticides. He must also consider the highly volatile chemicals, like *ozone* or the *halogens*

MERCURY. Compounds of mercury are used frequently, both in inorganic and organic preparations. Mercury behaves in vivo as an ion which reacts with *sulfhydryl* groups. Any enzyme featuring a sulfhydryl mechanism may be inactivated readily by surprisingly small amounts of mercury Both aerobic and anaerobic metabolism may be impaired by the mercuric ion Indeed, the union of mercury with a dissociable organic complex forms the basis for very effective diuresis Rapid renal excretion of such organic mercurial compounds assures quantitative accumulation only at the renal site Controlled, reversible poisoning of the renal tubule has been attained by the employment of this otherwise lethal heavy metal (mercury).

Circulating mercuric ion travels in an as yet undisclosed manner. Its deposition in tissue, likewise, is obscure. However, mercury does concentrate selectively in decreasing quantities in the kidney, liver, spleen, intestinal wall, heart, skeletal muscle, lung, and bone

Mercurial poisoning of the heart does *not occur* except with elemental mercury. A remarkable misunderstanding of this fact too often deprives patients of properly prescribed organic mercurial diuretics *Poisoning by inorganic mercury*, with its ability to disrupt myofibril metabolism and to cause "myocardial paralysis," may be counteracted by prompt administration of *BAL* (British antilewisite) and, more recently, by *Edathamil (EDTA)*.

ANTIMONY (STIBIUM). Only one inorganic compound of antimony is used as a drug. As in the case of mercury, substances containing antimony have been used extensively in medical practice, most especially as *emetics* (antimony tartrate) or *antiprotozoal* agents (ethylstibamine)

The *cardiac toxicity of antimony* is heralded first by marked *bradycardia* Electrocardiographically, definite abnormalities are recorded P-wave amplitude increase, *decline in* T-wave amplitude; lengthening of the Q-T interval, and aberrations of the S-T segment While these ECG abnormalities are reversible (and *anticipated* with antiprotozoal thera-

was normal The patient stated that, *since his accident*, he had suffered three chills and felt *feverish* following each chill. He also felt *nauseated*, and had vomited three times

Physical Examination. On admission to the military general hospital, examination *revealed* a well-developed, well-nourished *colored man who* did not appear acutely ill, but *who* was drowsy and lethargic The whole left upper extremity, from the finger tips to the axilla, was diffusely swollen, red, tense, and *tender. One* fang mark was seen over the proximal *dorsum of the* left thumb, and another *in the web* space between the thumb and index finger. *Both punctures* had been cut crosswise *by incisions* approximately one-fourth inch in length. There was no drainage from these incisions. Blood pressure was 108/80, pulse 84, respiration 20, and temperature 98 6°.

Laboratory Data. Laboratory findings were as follows*: hematocrit*, 55, leucocytes, 16,700 with 82 *per cent* polymorphonuclear cells; icteric index, normal, urinalysis *normal*, except for microscopic examination of the *sediment* which revealed rare *red cells*, occasional white cells, and rare granular and hyaline casts. Urinary urobilinogen was normal. The electrocardiogram was abnormal (Fig. 16-8).

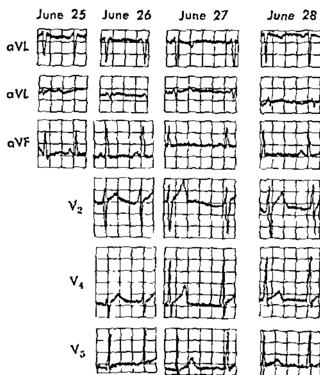


Fig. 16-8 Electrocardiogram of 38-year-old *Negro* male patient, victim of rattlesnake bite Whether the T-wave *variations displayed in* these selected electrocardiographic leads *have direct* myocardiopathologic significance *cannot be established* unequivocally, but the serial study *certainly* has merit. (Note especially leads aVF, V_2, V_4, and V_5.)

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TABLE 16-2. UNTOWARD CARDIOVASCULAR EFFECTS OF COMMONLY ENCOUNTERED CHEMICALS

Chemical	Cardiovascular effects
Aconite	Cardiac standstill
Atropine	[illegible] blood pressure elevation
Barium compounds	
Benzene	
Caffeine	
Camphor	
Chloral hydrate	Bradycardia, hypotension
Chlorates, bromates, nitrates	[illegible]
Chlorine	
Chloroform	
Cocaine	
Colchicine	
Ergot	
Iodine	
Lead, tetraethyl	[illegible]
Nitrites	
Phosphorus	
Physostigmine	
Salicylates (including aspirin)	[illegible]
Sulfur dioxide	
Thallium salts	
Tin salts	
Tobacco	
Turpentine	Tachycardia and hypotension

rhythm, on the other hand, should be considered *as due to* the disease process and *not* to a drug.

Electrocardiographically, discrete diagnosis of disturbances in the heart rhythm may be obtained, while evidence of conduction aberrations may also be disclosed Intraventricular conduction delay, complete bundle branch block, and lesser degrees of delayed conduction may be encountered as the result of any substance toxic to the cardiovascular system; frequently this includes such drugs as digitalis, quinidine, and procaine amide (Pronestyl).

DIAGNOSIS

Except for miscarried cardiac drug therapy, in which instances the medication is always the first suspect, the diagnosis of poisoning of the heart rests on sound conventional principles.

First, with evidence of cardiovascular malfunction, the more usual pathophysiologic possibilities must be eliminated, of course, the fact that the patient may also have preexisting organic heart disease must not be forgotten An accurate, detailed *history is* essential, particularly when the choice of powerful specific countermeasures is contemplated. The cardiac abnormalities present must logically be those known to be produced by the suspected noxious agent. Misappraisal here can spell disaster.

Once it has been established that probably no other cause for the cardiotoxicity exists, the *singular* therapy indicated may be justifiably initiated *Drugs* tending to aggravate an *already* toxic myocardium must be avoided. A [illegible] will have to be directed at the organism as a whole, rather than at the heart as an independent organ Specific cardiac medication is generally a secondary consideration to the institution of fundamental "antitoxic" measures

RATIONALE FOR [illegible]

The clinical status of the patient's heart will be reflected directly by the extent, nature, and site of any poisoning process involving the cardiovascular *system* directly or indirectly. Whether cardiac functional capacity *remains* intact or is fatally impaired depends on the

peutic objectives) still it must be remembered that the blood vessels are affected seriously all over the body. In the myocardial vascular mesh, this implies *multifocal hemorrhages*. Obviously, then, *myocarditis* other than that of protozoal origin, becomes an absolute contraindication for the use of antimonial compounds.

GOLD. The usurer's mania is prescribed today almost exclusively for the amelioration of rheumatoid arthritis. It has *no outstanding effect on the cardiovascular system;* its toxicity is directed rather, to the hematopoietic system. Whether its pronounced ill effects upon aged and senile persons are due exclusively to gold's acknowledged toxicity to most organs *other than* the heart, is not known, but certainly elderly individuals do not tolerate gold.

SILVER. "Heart disease" due to silver really has nothing to do with cardiovascular disorders. The phrase has been applied to individuals with *argyria*, mistakenly thought to have heart disease because of their cyanotic appearance. Any valid use of silver in medical practice should be limited to local applications only, because of the effective antiseptic and germicidal properties of the silver ion Inorganic salts, usually the nitrate, or organic protein combinations are procurable. Even when silver arsphenamine was widely used, the drug apparently had little effect on the cardiovascular system. The severe *bradycardia* produced by silver compounds injected into animals is apparently of central vagal origin.

PLATINUM. Platinum produces chest distress ("tightness," dyspnea, etc) which requires differential diagnosis to establish pathologic changes in the pulmonary system as the cause, rather than coronary arterial disease or congestive heart failure Also it is necessary to realize that this widely used metal has industrial and social significance in today's environment. At times, the indispensable soluble complex salts of platinum (sodium chloroplatinate) cause enigmatic clinical diagnostic problems of major importance.

Cardiovascular poisoning by platinum is unreported to date, but the importance of this metal to other body systems of the human organism is indisputable.

British anti-lewisite, or *BAL* (2,3-dimercaptopropanol), was developed during World War II for use in the treatment of lewisite poisoning. Besides being an effective antidote for arsenic poisoning, it is also a potent agent against intoxication by other heavy metals, e g, gold, cadmium, and mercury; it is not effective against lead. Evidence of its usefulness has been suggested in poisoning due to antimony, chromium, nickel, copper, zinc, and bismuth Instantaneous administration is imperative, *BAL* must be used *intramuscularly—never intravenously*. It is used as a 10 per cent solution in peanut oil, which also contains 20 per cent benzyl benzoate.

Untoward cardiovascular reactions to BAL itself consist of (1) tachycardia, (2) increased arterial blood pressure, (3) sensations of diffuse warmth, and (4) diaphoresis. Such unwanted side effects are usually dissipated within 30 to 180 min. Their interim amelioration is effected with barbiturates or other symptomatic medication.

CLINICAL ASPECTS

Symptoms. Profound weakness, easy fatigability, and dyspnea on slight exertion tend to be the chief complaints of the patient suffering from any type of "poisoning" of the heart. Essentially, the degree of suffering is related directly to the extent of myocardial involvement, particularly since intoxication of the myocardium affects the heart as a pumping organ.

Precordial discomfort, ranging from an indescribable annoyance to "missed beats," "thumping," or the like, may be experienced if arrhythmias have been produced by the noxious agent. *Anxiety*, associated with any of these complaints, is a complication related largely to the psyche, rather than one produced by the cardiac lesion itself. If *heart failure* is present, naturally the "central" cerebral anxiety tends to be evident.

Objective Findings. Intoxication of the heart can produce all the various clinical signs one would expect with any of the more ordinary pathological changes, i e, congenital, rheumatic, or hypertensive. Disturbances of the normal pacemaker are quite apt to occur, especially minor abnormalities like premature ventricular or atrial contractions In fact, if digitalis is being administered and the rhythm becomes altered after initiation of therapy, the drug, rather than a disease process, should be suspected because it so commonly induces premature contractions or AV block A *triple*

9

Cardiovascular disturbances in neuromuscular dystrophies

Pathological Aspects
C. GEORGE TEDESCHI

Clinical Aspects
ELWYN EVANS

PATHOLOGICAL ASPECTS

It is generally acknowledged that many anatomically unrelated congenital defects may have a common underlying mechanism in a genetic or prenatal environmental disorder. The association of developmental cardiac anomalies with anatomical defects in other organs and systems is well documented by observations in human beings and by the recent demonstration of a multiplicity of organic defects in the offspring of animals exposed during gestation to varieties of injuries Less clearly understood is the more subtle disturbance that underlies the association of dystrophic disorders in the heart and those in some other organ or system. This sort of relationship is suggested by the high incidence of cardiac alterations in at least two neuromuscular dystrophies. Friedreich's ataxia and progressive muscular dystrophy.

FRIEDREICH'S ATAXIA

Newton Pitt (1887) pointed out heart failure as one of the manifestations of the last phases of a case of Friedreich's ataxia However, when Evans (1942) showed electrocardiographic changes in 12 of 38 patients affected by this disease, it became apparent that cardiac disorders are common in this neurological condition Russell substantiated Evans' observations and showed that the cardiac functional disorder is associated with a structural disturbance, mainly characterized by focal degeneration of muscle fibers; moderate, unevenly distributed inflammatory cell infiltration (lymphocytes, eosinophils, neutrophilic leucocytes); and fibrosis and hypertrophy of the surviving fibers. The Purkinje fibers of the AV node and of the bundle of His were similarly separated by fibrous tissue and inflammatory cells. He concluded that the same agent, possibly of toxic origin, had been responsible for both the cardiac and the neurological lesions Manifestations of cardiac disorder were the patient's major complaints in two cases of Friedreich's ataxia described by Manning In one patient, a 24-year-old man, the heart weighed 705 Gm, in the absence of valvular lesions, coronary artery disease, or any other plausible explanation, the myocardium showed diffuse fibrosis, hypertrophy of remaining myofibrils, and scanty lymphocytic infiltration Since available information indicates that cardiac manifestations occur in approximately one-third of the cases of familial Friedreich's disease, it is conceivable that an inherited lethal gene is responsible for both the cardiac and neural disorders.

PROGRESSIVE MUSCULAR DYSTROPHY

Dystrophic myocardial lesions also occur in progressive muscular dystrophy and they bear a resemblance to the lesions of the skele-

factors listed above. Disruption of the myofibrillar mesh is the key to dysfunction of the heart as an efficient pump. Any toxin, noxious substance, or innocuous material (poisonous because of its excess) will inactivate cardiovascular functions to a degree comparable to the poisoning of other vital organs. The manifold abnormalities of heart disability, from minor ECG aberrations to lethal acute congestive heart failure, are detailed appropriately elsewhere (Part 8, Chap. 9).

The basic principle, then, in approaching the evaluation of the "poisoned heart" is simply to determine whether *each and every myofibril is intact, is affected reversibly, or is permanently damaged.* Sensible therapy is based fundamentally upon accurate appraisal of this problem.

CHOICE OF SPECIFIC CARDIOACTIVE DRUGS

When one is dealing with arrhythmias of the *diseased* heart, two further basic questions arise: (1) is the mere presence of the arrhythmia itself potentially lethal; and (2) is the rapid ventricular rate associated with the abnormal rhythm the important factor which may contribute to increased morbidity, or even cause the death of the patient? Obviously, prior knowledge of the nature of the arrhythmias is necessary in order to make these judgments but, if this is understood, then the problem of treatment is clear and simple.

Choice of Drug. To dispose of the second problem first, if the rapid ventricular rate alone constitutes the threat to life, there is actually no choice of therapeutic agent. There is only *one* cardiac drug (actually, group of drugs) which will decrease the ventricular rate consistently, dependably, and invariably: digitalis.

The problem of cardiac arrhythmias has now been narrowed down to the group in which the arrhythmia itself possesses inherent fatal possibilities. These arrhythmias are predominantly ventricular in origin, i.e., multifocal premature contractions, ventricular tachycardia, or ventricular fibrillation. Other disturbances of rhythm are essentially caused by atrioventricular or intraventricular conduction disturbances and are abnormalities of impulse propagation.

Almost all ventricular arrhythmias can be treated with one of two drugs: (1) *Pronestyl* (procaine amide) and (2) *quinidine*. Pronestyl usually is the drug of choice, most particularly if there is an intraventricular conduction defect, although Pronestyl itself can cause such a change. Procaine amide has the marked disadvantage of being a potent hypotensive drug and must be given parenterally with extreme caution. Quinidine, to be effective, requires doses so large as to induce undesirable side effects. Either drug should be used parenterally *only* with continuous electrocardiographic control, and particular attention must be paid to their extreme propensity for causing delayed stimulus transmission. The marked hypotensive effect of Pronestyl can be combated successfully with pressor agents, like *Levophed* or *Vasoxyl.*

tion, first appears in the *lower* extremities and gradually extends to the rest of the body. The patient tends to walk with a broad base and is unsteady. Spontaneous irregular movements, of the head, shoulders, and extended limbs, occur. Hypotonia or spasticity, and present or absent tendon reflexes, depend upon relative involvement of the posterior columns and the pyramidal tracts. The Babinski and Romberg signs are usually positive. There *may* be skeletal deformities, especially scoliosis. The feet are characteristically shortened, the longitudinal arches high, and toes hyperextended, especially the great toe. Nystagmus and speech disturbances are characteristic. The speech may be slow, scanning, or staccato, and sometimes explosive. Sensory changes are uncommon.

Cardiac involvement in Friedreich's ataxia *is frequent*. Evans and Wright found it to be present in 30 per cent of 38 patients. Manning found heart involvement in four patients with neurological evidence of Friedreich's ataxia, but *found none in two* patients with variants of the disease. Lorenz et al found typical heart involvement in five siblings.

The cardiac symptoms most often described are tachycardia, palpitation, and dyspnea. Definite evidence of *congestive failure* appears in some cases, especially late. Schilero et al mentioned precordial pain and stated that *myocardial infarction* had been noted in one instance. Hejtmancik et al (1949) described two patients with mitral diastolic murmurs confirmed by phonocardiographic tracings. Heart murmurs, including diastolic murmurs, had been described previously by Friedreich and others. Cardiac irregularities and tachycardia have been mentioned frequently and paroxysmal tachycardia or atrial fibrillation occasionally.

Electrocardiogram. The electrocardiogram is frequently abnormal in Friedreich's ataxia. Guillain and Mollaret, Laubry and Heim de Balsac, and others have emphasized electrocardiographic changes, especially changes in rhythm. Electrocardiographic abnormalities were noted in twelve of the 38 cases reported by Evans and Wright, in all four of Manning's patients with obvious neurological findings of Friedreich's ataxia, but not in the two with variants of the disease, and in all five siblings reported by Lorenz et al.

Even the electrocardiogram seemed to show some familial similarities. Lorenz et al commented that the tracings of *five siblings* had a marked resemblance to each other, to those of their father, and to those in the literature. Four of the children showed inversion of the T waves in leads II, III and V_6; one child and the father showed low T waves without significant inversion. Peaked T waves and prominent S waves were present in *all five* siblings, and right axis deviation was present in two. In the literature, ectopic beats, atrial and ventricular, were frequent, paroxysmal tachycardia was not uncommon, and atrial fibrillation was only occasionally mentioned.

Roentgenography. Left ventricular enlargement was noted in 25 per cent of the cases reported by Evans and Wright; three out of four cases reported by Russell, and three out of five cases reported by Lorenz et al. Enlargement of the heart was *frequently noted in the* literature.

Diagnosis. Diagnosis depends upon the recognition of cardiac signs and symptoms in the presence of neurological evidence of Friedreich's ataxia. The hereditary and familial patterns are helpful. Recognition of cardiac involvement depends to a great extent upon the electrocardiographic *picture* of T-wave changes, with or without cardiac irregularities. The absence of a history of rheumatic fever in the patient or family and the absence of left atrial enlargement on fluoroscopy, help rule out rheumatic valvular heart disease, which frequently is suggested by the presence of an apical systolic murmur and occasionally by an apical diastolic *murmur*.

Prognosis. The prognosis in general is poor. The picture may remain stationary for long periods, but the general course *is slowly progressive* to complete incapacity, unless it is cut short by acute myocardial failure or intercurrent infection.

Treatment. There *is no* specific treatment. Myocardial failure, of course, should be *treated* by the usual measures, and occasionally *it may* be *relieved dramatically* by treating an acute tachycardia which *responds* to therapy.

FAMILIAL CARDIOMEGALY

At this point, it may be well to mention the familial cardiomegaly *described* by Evans, who found cardiac enlargement to be familial in *some cases*. Clinically, it was often found fortuitously in *young* adults during routine examinations, or when they were examined

tal muscles Since this is not a disease of great rarity (over 200,000 patients are listed by certain organizations in the United States), and heart involvement is reported in 50 and 85 per cent, respectively, of the cases reviewed in two different series, *the cardiac component of progressive muscular dystrophy must be viewed as a condition of some importance.* There is a general consensus that involvement of the heart muscle plays a role in the course of the disease and that, in many instances, it is responsible for the fatal event.

Cardiac histopathologic changes are nonspecific and depend on the duration and severity of the myocardial lesions. The epicardium and valvular endocardium usually are not implicated and the coronary arteries are not involved. The endocardium lining the ventricles may be slightly thickened, and the myocardium is often scarred in an irregular, patchy manner. Microscopically, individual muscle fibers and bundles of muscle fibers are seen to be entrapped by the proliferated collagenous tissue and the involved myofibrils often show atrophy, vacuolation, and fragmentation. Degenerative changes in the myofibrils may be seen independently of fibrosis, and a few lymphocytes and phagocytic macrophages are often noticed in their proximity. In view of the great similarity of the changes, it can be assumed that the disturbance reflects a systemic dystrophic state of the striated muscle

DYSTROPHIA MYOTONICA

In dystrophia myotonica, abnormalities of the cardiovascular system have received attention, but their significance is not as yet clearly understood The chief abnormality is a disturbance of conduction, either from the atria to the ventricles, or within the ventricles. Carrot et al. have postulated an abnormality at the neuromuscular junction. Londres, in the necropsy of a patient with abnormal electrocardiographic patterns, observed histological changes in the myocardium similar to those in the skeletal musculature. Apparently, this single observation has not as yet been duplicated. Furthermore, Black and Ravin could not find significant deviations from the normal in the hearts of five patients with dystrophia myotonica, who died from several different causes.

CLINICAL ASPECTS

FRIEDREICH'S ATAXIA

Pathogenesis. The basic cause of this disease is obscure; but it is known to be hereditary and often familial. The basic origin of the cardiac involvement is also unknown, however, this too has definite familial tendencies (Evans and Wright, Manning, Lorenz et al.)

Pathologic Changes. There is degeneration of the posterior columns, the pyramidal tracts, and the spinal cerebellar tracts, together with secondary gliosis The spinal cord and the cerebellum may be smaller than usual

Although several authors, including Friedreich himself, described cardiac symptoms and signs, Pitt was the first to emphasize cardiac involvement, and the first to describe myocarditis unassociated with acute terminal illness Russell (1946) described chronic interstitial myocarditis in four patients with Friedreich's ataxia, three of whom showed marked cardiac hypertrophy. Microscopically, there was focal destruction of muscle fibers, fatty degeneration of muscle fibers, and fibrosis and hypertrophy of the surviving muscle fibers. There was some scattered infiltration with small lymphocytes and a few eosinophils and neutrophils Russell mentioned diffuse atheromatous change in the coronary arteries of one patient and slight involvement in another. Congestion and fatty degeneration of the liver and kidneys were mentioned in three instances Schilero et al. stated that the following pathologic picture of the heart was almost invariably present: (1) hypertrophy of all chambers, especially the left ventricle, (2) diffuse interstitial fibrosis of the myocardium; (3) fatty degeneration of the myocardium; (4) round cell infiltration with lymphocytes and eosinophils, (5) normal endocardium and valves; and (6) coronary arteries varying from normal to diffusely atheromatous. They also stated that the following were occasionally seen: (1) pericardial effusion, (2) fibrous pericardial thickening, (3) epicardial petechiae and hemorrhages, and (4) cardiac dilatation.

Clinical Picture. Neurological symptoms usually appear at or near puberty. Ataxia, or incoordina-

pertrophy. The contrast in muscle size and strength is striking Pseudohypertrophy is common in the younger patients, but uncommon in older ones Eventually, most of the muscles are involved, atrophy replaces hypertrophy, and in the late stages, lipodystrophy is frequent, with large deposits of fat about the face, neck, hips, and thighs.

Characteristically, there is weakness and clumsiness The patient has difficulty getting up from a horizontal position, he has to turn face-downward to raise his body on his hands and knees, and then "climbs up on himself." Lumbar lordosis is increased on standing Pain is not prominent. The gait is awkward and waddling. Contractures develop sooner or later in most patients Tendon reflexes are diminished or absent There may be recurrent bouts of fever.

The most prominent cardiac symptoms are related to the cardiac arrhythmias (Zatuchni et al.). Patients may feel well, but then suddenly experience palpitation, feel sick, and break out in a cold sweat, sometimes with associated vomiting, abdominal pain, or a shocklike state. A few patients may be dyspneic, but swelling of the legs is rare Associated myocardial failure tends to be predominantly left ventricular.

Heart size was mentioned clinically in 38 of 94 cases; in six instances the heart was enlarged (Zatuchni et al) Heart sounds usually were of good quality, but the 1st apical sound at times was feeble, and the 2d pulmonic sound, accentuated A systolic murmur was usually present at the base or, especially, the apex. Heart rate or rhythm was mentioned 27 times, the rate varying from 80 to 180 per minute Eight patients experienced irregular pulse or periods of tachycardia.

Boas and Lowenburg studied the heart rate with a cardiotachometer in seven patients, and found the heart rate to be elevated in each during sleep as well as in his waking hours

Technical Studies. ELECTROCARDIOGRAM Observations were recorded in 105 instances reviewed by Zatuchni et al. There was usually a rapid sinus rhythm, although ectopic beats, atrial or ventricular, were not uncommon Two patients had paroxysmal ventricular tachycardia The P-R interval was normal in all but three instances. The duration of the QRS complex was lengthened in three instances, nd the Q-T interval lengthened once. Although Q waves were frequently mentioned in leads II and III, there were no abnormally wide Q waves in any of the 105 cases. Rubin and Buchberg found definitely abnormal Q waves in two cases The Q waves were present in leads I, aVL, and in some of the precordial leads One patient was a 19-year-old boy in congestive failure.

ROENTGENOGRAM. In the cases in which heart size was mentioned, it was usually normal, but not uncommonly slightly enlarged Conspicuous streaking of soft-tissue shadows may be noted in affected muscles (Shank et al).

BLOOD STUDIES. Blood creatine is usually increased, but blood creatinine is normal (Shank et al). The sedimentation rate is usually elevated.

BASAL METABOLISM The B.M.R. is consistently low; the median level for 14 patients was minus 14 5 (Shank et al).

URINALYSIS. The rate of creatinine excretion is less than normal, and that of creatine is greater than normal, especially in boys The ability of the muscles to retain ingested creatine is impaired, and the creatine tolerance is low.

Diagnosis. In most cases, diagnosis of progressive muscular dystrophy is not difficult because of the posture, gait, pseudohypertrophy, impairment of creatine metabolism, lack of a reaction of degeneration, and absence of fasciculation These findings help to differentiate it from the progressive muscular atrophies involving the nervous system. Frequently, congenital heart disease or scoliotic heart disease must be considered in the differential diagnosis because of the age of the patient or the presence of spinal or chest deformities. Zatuchni et al described a 30-year-old patient who was thought to have idiopathic cardiomegaly until the underlying progressive muscular dystrophy was apparent after compensation was established. Occasionally, gastrointestinal symptoms predominate and diagnosis may be difficult if other signs are not present.

Prognosis. The eventual outlook is poor, because atrophy and weakness progress The immediate prognosis depends upon the extent of heart involvement The course is generally more rapidly progressive when the onset oc-

because of cardiac enlargement, minor symptoms, or abnormalities in a routine electrocardiogram.

Findings, including electrocardiograms, were similar to those found in cases of Friedreich's ataxia with cardiac involvement, but without neurological evidence of the disease.

Prognosis in these cases depended to a great degree upon the extent of heart involvement; however, sudden death sometimes occurred from acute failure precipitated by paroxysmal tachycardia.

Manning is of the opinion that these cases probably are examples of Friedreich's disease without neurological manifestation.

PROGRESSIVE MUSCULAR DYSTROPHY

Progressive muscular dystrophy is one of the chronic, progressive, degenerative myopathies; it is characterized by atrophy and weakness of certain muscle groups, creatinuria, and at times pseudohypertrophy.

It is variously classified, depending upon the muscle groups initially and most severely affected, and the presence or absence of pseudohypertrophy, but the main clinical and pathologic features are similar in all forms.

Origin. Other than that the disease is hereditary and familial, the cause is unknown. About 45 per cent of the patients give a history of at least one other member of the family being affected with the disease. Heredity in the pseudohypertrophic form is usually by means of a recessive factor, often sex-linked; heredity in the facioscapulohumeral form is usually by means of a dominant factor. It occurs about three times as often in males as in females.

Cardiac involvement has been considered part of the picture of progressive muscular dystrophy because of its frequent association with this disease and the similarity of the myocardial changes to those of the skeletal muscles (Weisenfeld and Messinger). Globus summarized necropsy findings of the heart in 10 cases in 1922, and Zatuchni et al. reviewed 292 cases of progressive muscular dystrophy reported from 1922 to 1951 and found that 94 were reported to have some cardiac abnormality. Rubin and Buchberg stated that the heart was involved in about 50 per cent of their 33 cases. Of 44 cases (Weisenfeld and Messinger), 85 per cent had some clinical evidence of cardiac dysfunction.

Pathologic Changes. Although many structures are involved, the muscular involvement is characteristic: skeletal, cardiac, and gastrointestinal. All four cases described by Bevans showed skeletal, cardiac, and gastrointestinal muscular involvement. The myocardial changes are somewhat similar to those found in the skeletal musculature, so only myocardial changes will be described.

Zatuchni et al. found reports of 19 patients on whom autopsies were performed. The weight of the heart, in the seven instances in which it was recorded, varied from 140 to 600 Gm. Dilatation was present in four, and hypertrophy in one case. Epicardial fat was grossly present in some instances, and at times fat invaded the myocardium. Occasionally areas of heart muscle were replaced by connective tissue. Grayish streaks were usually noted in the ventricular wall, and small fibrotic areas were often seen. Occasionally, the endocardium was slightly thickened. The valves and vessels were not involved in the series of Zatuchni et al., but atheromas of the coronary vessels were mentioned by Bevans and by Storstein and Austerheim.

Microscopically, myocardial fibrosis varied from finely diffuse sclerosis to large areas of scarring. Fatty infiltration was usually present, and edema involved all structures. Muscle fibers varied in size; atrophy predominated, but some fibers were hypertrophied. There was fragmentation and loss of striation. Some fibers were degenerated and replaced by connective tissue. No evidence of specific inflammatory reaction was noted.

Clinical Description. The disease usually appears early in life. Of 44 cases, the first symptoms appeared before the age of 10 in 62 per cent; indeed most of the symptoms appeared before 5 years of age, but in a few instances were delayed until the patient was as old as 50 (Shank et al.).

In the juvenile type of this disorder, the muscles of the shoulder girdle are involved first. In the facioscapulohumeral type, the muscles of the face, shoulder girdle, and arms are involved first. In the latter group, patients have a "transverse" smile because the corners of the mouth cannot turn up. Shank et al. reported macroglossia in five patients of this group. In the pseudohypertrophic type, muscles of the lower extremity are usually involved first, and the calf muscles are large and feel hard because of hypertrophy and pseudohy-

interval was prolonged in 48.3 per cent, QRS complexes prolonged in 11.7 per cent, and low T waves were present in 3.5 per cent. There was one case each (1.2 per cent) of transient atrial fibrillation, transient atrial flutter, left ventricular preponderance, and nonspecific S-T changes. Litchfield described a case with Stokes-Adams attacks which were thought to be due to the onset of an abnormal ventricular rhythm in the course of AV dissociation

ROENTGENOGRAMS Of 85 cases (Fisch), the heart was enlarged in ten; enlargement was slight in three instances, moderate in five, and marked in two

METABOLIC STUDIES The B M R is consistently low, but in eight cases studied in detail by Jacobson et al and by Holland and Hill, there were no other endocrine abnormalities except slightly decreased 17-ketosteroid secretion. The blood cholesterol, radioactive iodine uptake, serum protein-bound-iodine levels, and response to administration of thyroid stimulating hormone (TSH) were consistently normal, so these authors concluded that the low B.M R was extrathyroidal and probably due to reduced muscle mass.

ELECTROPHORESIS Studies reveal a tendency to elevated beta globulins and low gamma globulin, the latter increases upon antigenic stimulation, according to Zimmerman and Rotstein

Diagnosis. Myotonia distinguishes dystrophia myotonica from the other dystrophies or atrophies, as well as from Addison's disease Hypothyroidism with myotonia possibly should be considered, but atrophy and the other laboratory tests should eliminate this Cardiac involvement should be suspected if symptoms of heart disease arise in a patient with dystrophia myotonica, or if there are electrocardiographic changes, especially conduction defects, and particularly AV conduction defects

Prognosis The course is insidiously progressive

Treatment No therapy affects the course of the disease, but myotonia may be fairly well controlled. Cortisone and corticotropin significantly reduced the duration of myotonia in eight of nine patients and virtually abolished it in three. Quinine was less effective but of definite value in relieving the myotonia (Liversedge and Newman).

MYASTHENIA GRAVIS

Myasthenia gravis is a chronic neuromuscular disease characterized by extreme muscular fatigability.

Origin and Pathogenesis. The precise cause of the disease is obscure, although it is known that symptoms result from an interference with the transmission of impulses across the myoneural junction associated with disturbed acetylcholine metabolism.

Pathologic Changes. Pathologically, the most frequent change has been the focal infiltration of striated muscle with groups of lymphocytes (and a few epithelial cells), called lymphorrhages. The first investigators to mention myocarditis as an integral part of myasthenia gravis were Rottino et al. who reported a case of thymoma with myocardial necrosis associated with acute and chronic inflammatory reaction Subsequently, Russell (1953) described myocardial necrosis and inflammation in three of six cases in which the myocardium was studied microscopically, and mentioned the parallelism between myocardial and striated muscle lesions in type and degree. Mendelow and Jenkins studied autopsy material, with special reference to myocardial involvement, in 12 consecutive cases of myasthenia gravis, thymoma, or both, and found histologic foci of myocardial necrosis of varying degrees in six. The pronounced myocardial changes appeared in the only three instances of malignant lymphoma

Clinical Picture. Clinically, myasthenia gravis is characterized by undue muscle fatigability, especially of the ocular muscles Sustained or repeated stimulation causes rapid fatigue Frequently, the muscles of deglutition and phonation and those of the extremities are involved There may be a nasal quality to the voice, and swallowing may be difficult. With the involvement of the flexors of the extremities, foot drop occurs. Involvement of the flexors of the head may cause the patient to have difficulty in raising the head when lying down and necessitate his supporting his head with his hands when sitting Generalized weakness or asthenia was present in 25 of 60 patients reported by Garland and Clark.

Despite the fact that dyspnea and often cyanosis have been prominent in severe and fatal cases of myasthenia gravis, only one significant clinical study has been made with

curs before the age of 5 years. The duration of the illness ranged from 2 to 65 years in 44 cases reported by Weisenfeld and Messinger.

Treatment. There is no specific treatment for progressive muscular dystrophy, but associated myocardial failure or cardiac irregularities should be treated by the usual methods: digitalis, salt restriction, diuretics, and so forth.

DYSTROPHIA MYOTONICA (MYOTONIA ATROPHICA)

Dystrophia myotonica is a chronic progressive disease characterized mainly by myotonia and atrophy of certain muscle groups, and by lens opacities.

Causative Factors. Dystrophia myotonica is a familial disorder with a dominant hereditary characteristic, but the basic cause is unknown. It occurred in six members of one family (Holland and Hill), and in three of six siblings who lived long enough to manifest the disease (Black and Ravin). Glandular dysfunction frequently has been thought to be a factor, but with careful metabolic studies, no such dysfunction could be revealed (Jacobson et al.; Holland and Hill).

Pathologic Changes. The literature has revealed inconstant changes in the central and peripheral nervous systems and in the endocrine glands, except for the testes which have frequently shown atrophy. Testicular atrophy was present in all four cases of Black and Ravin, almost complete in three of them. Striated-muscle changes are characterized by striking atrophy of the muscle fibers. Late changes include fibrosis and fatty tissue replacement. Fisch (1951) stated that, so far as the heart was concerned, anatomic studies were so meager that no definite opinion could be expressed. Of five cases, Black and Ravin found no cardiac changes in three, increased lipochrome pigment in the myocardium in one, and moderate variability in size of myocardial fibers in the other. Fisch and Evans described a case showing moderate fatty infiltration, marked diffuse fibrosis, and scattered hypertrophied muscle fibers with large rectangular nuclei.

Clinical Description. Symptoms usually begin at about twenty to thirty years of age, but may appear earlier. Atrophy is a prominent feature and [illegible] the orbicularis oculi and oris muscles, masseters, sternocleidomastoids, dorsiflexors of the feet, and muscles of the forearms and thighs. Atrophy may be extreme, especially of the sternocleidomastoid. Facial muscle involvement produces an expressionless appearance, the *myopathic facies*. Involvement of the dorsiflexors of the feet causes foot drop. Atrophy becomes generalized as the disease develops; this, and the associated weakness usually are the motivating reasons for seeking medical advice.

Myotonia also is characteristic. A prolonged muscular contraction or delayed relaxation occurs after voluntary, mechanical, or electrical stimulation. Myotonia is usually most pronounced in the muscles of the hand and forearm, although other groups may be involved.

Other characteristics are frontal baldness, testicular atrophy, cataract, and low basal metabolic rate. Cataracts may appear at an early age, and evidence of heredity of this condition may be limited to their presence.

Griffith (1911) is given credit as being the first to focus attention on the heart when he described a patient with bradycardia as low as 36 beats/min. Fisch (1951) reviewed 85 cases of dystrophia myotonica including six of his own patients, and stated that, with few exceptions, in cases in which the heart was involved, there was an almost complete absence of clinical history and the heart was inadequately examined. Only reports in which electrocardiographic data or anatomical or roentgenographic studies of the heart were available, were included in this study. In only 6 of 85 patients were the symptoms of the heart so severe as to be presenting symptoms. In two out of five of Fisch's patients, the presenting symptoms were exertional dyspnea and palpitation, respectively, and in two of Evans' patients (1944), the presenting symptom was exertional dyspnea. Of 85 patients, the pulse rate was below 50 per minute in nine patients and below 60 in four more. The systolic blood pressure was less than 100 mm Hg in 13 patients and less than 110 in 14 more. Only three patients had systolic pressures above 140. Soft apical systolic murmurs, thought to be functional, were mentioned in ten instances, split 1st apical sounds in eleven, and distant sounds in seven.

Technical Studies. ELECTROCARDIOGRAM. Of 85 cases reviewed in the literature, electrocardiograms were found to show some abnormality in 68.3 per cent (Fisch). The P-R

Cardiac dilatation, systolic murmurs, bradycardia, and electrocardiographic changes may occur during an attack.

Technical Studies

BLOOD CHEMISTRY. Biemond and Daniels first found the serum potassium level to be low during spontaneous attacks. Aitkin et al. confirmed these findings, and noted the prompt beneficial effect of potassium administration; however, there has been no constant correlation between serum potassium levels and paralysis Watson and other investigators have observed cases in which paralysis occurred when serum potassium levels were normal, and these were not benefited by potassium administration.

ELECTROCARDIOGRAM. Electrocardiographic changes in familial periodic paralysis are similar to those occurring with hypopotassemia Initial electrocardiographic observations in hypopotassemia were made on patients with familial periodic paralysis (Stewart and Milhorat; Stoll and Nisnewitz), although electrocardiographic changes had been noted previously in conditions causing hypopotassemia.

Bellet et al made extensive studies on 79 patients with hypopotassemia, one of whom had familial periodic paralysis, and confirmed the changes ascribed to hypopotassemia by Holler and other workers There was no pathognomonic pattern, five electrocardiographic patterns were observed. The changes were predominantly in the T waves, S-T segments, Q-T intervals, and U waves. The five patterns of S-T and T-wave changes associated with Q-T–segment prolongation consisted of the following: (1) depression of the S-T segments in varying degrees; (2) inversion of the T waves, (3) T waves of normal amplitude; (4) T waves of low amplitude; and (5) prominent U waves following the T waves. Eighty per cent of the records fell in the first two groups The electrocardiographic changes were immediately reversible following administration of potassium. The U wave was present in 42 per cent of the cases studied.

Diagnosis. Diagnosis depends upon the discovery of hypopotassemia, electrocardiographic changes, or both during episodes of paralysis, and a return to normal with the administration of potassium.

Prognosis. The condition may last for years. *Occasionally*, death may occur during an attack. Sometimes the attacks tend to decrease with age.

Treatment. Treatment consists of oral or intravenous administration of potassium for the acute attacks, and 4 to 6 Gm of potassium chloride orally as daily prophylaxis.

reference to the cardiovascular system (Taquini et al., 1940). This covered 14 patients with proved active myasthenia gravis and the authors recorded venous pressures, circulation times, electrocardiograms, orthodiagrams, and the effect of carotid sinus pressures. They also studied the effect of Mecholyl in ten instances, and the effect of atropine in nine. They had the opportunity of making pathologic studies on one of these patients and on two others, and concluded that there was no clinical or pathologic evidence of heart involvement in the patients studied

Mendelow and Jenkins mentioned that thorough clinical cardiac evaluation had not been made in the 12 cases they studied pathologically because of the certainty of the clinical diagnosis of myasthenia gravis.

Technical Studies. ELECTROCARDIOGRAM. The electrocardiogram was normal in 14 active cases of myasthenia gravis reported by Taquini et al. Of four cases which came to autopsy and in which electrocardiograms were mentioned, two electrocardiograms were normal; one showed depressed S-T segments in leads I and II; depressed T waves in leads I, II, and III, and inverted T waves in lead IV; the other showed diphasic T waves in V_2 and elevated S-T segments in V_1 through V_6 (Mendelow and Jenkins).

BLOOD STUDIES. A curare-like substance has been found in the blood of patients with myasthenia gravis (Wilson et al., 1953).

ROENTGENOGRAPHY. Orthodiagraphic studies of the heart in 14 active cases revealed no abnormalities (Taquini et al.). Chest roentgenograms were mentioned in only one of fourteen cases reported by Mendelow and Jenkins, and these were normal. Roentgenograms may reveal thymic enlargement, but this is often difficult to diagnose unless tomography is used (Harper) Despite the diagnostic difficulties, thymic enlargement should be looked for in each instance

Diagnosis. Diagnosis of myasthenia gravis in typical cases usually is not difficult, but diagnosis in mild cases, especially those with localized symptoms, may be difficult. Diagnosis depends upon awareness of the disease, history of undue fatigability, physical findings, especially of ptosis or nystagmus, and response to medication. Symptoms improve quickly with intramuscular or intravenous administration of neostigmine or intravenous injection of Tensilon.

Prognosis. Prognosis, in general, is relatively poor. Of 202 patients followed for periods of 1 to 34 years, 32 per cent died within an average of six years after onset of symptoms, but 25 per cent had complete or nearly complete remissions lasting up to 17 years (Grob). Patients who have only ocular symptoms by the end of a year after the onset of symptoms are not likely to develop other evidence of the disease (Grob; Garland and Clark; Ferguson et al.).

Treatment. Medical therapy of myasthenia gravis at present utilizes neostigmine with ephedrine and occasionally quinidine or atropine. Infections should be treated strenuously and sedatives should be used cautiously The value of thymectomy and x-ray therapy is questionable (Vietz). Thymic x-ray therapy followed by thymectomy is thought to be of value (Williams, 1952.)

PERIODIC FAMILIAL PARALYSIS

Periodic familial paralysis is a hereditary and familial disease characterized by recurrent attacks of flaccid paralysis affecting the muscles of the extremities and trunk.

Origin. Other than the hereditary factor, the cause of the disease is not known, it is known to be associated with abnormal potassium metabolism and possibly abnormal carbohydrate metabolism, both of which affect muscle cells. About 80 per cent of the cases of periodic paralysis are definitely familial, but similar spells may be precipitated by conditions which lower serum potassium levels and by metabolic disturbances such as hyperthyroidism (Kepner).

Pathologic Changes. No anatomic abnormalities have been described

Clinical Description. Symptoms usually begin during the first or second decade of life. The attacks of paralysis are flaccid, involving the skeletal muscles beginning in the extremities and moving to the trunk Typically, the patient awakes during the early morning hours and finds he is unable to move. Attacks last, on an average, 6 to 8 hr, but may be shorter, or last several days

Characteristically, there is depression or loss of deep reflexes, normal sensory perception, and no loss of consciousness during attacks Patients feel well between attacks.

Cardiac dilatation, systolic murmurs, bradycardia, and electrocardiographic changes may occur during an attack.

Technical Studies

BLOOD CHEMISTRY. Biemond and Daniels first found the serum potassium level to be low during spontaneous attacks Aitkin et al. confirmed these findings, and noted the prompt beneficial effect of potassium administration, however, there has been no constant correlation between serum potassium levels and paralysis Watson and other investigators have observed cases in which paralysis occurred when serum potassium levels were normal, and these were not benefited by potassium administration

ELECTROCARDIOGRAM. Electrocardiographic changes in familial periodic paralysis are similar to those occurring with hypopotassemia Initial electrocardiographic observations in hypopotassemia were made on patients with familial periodic paralysis (Stewart and Milhorat, Stoll and Nisnewitz), although electrocardiographic changes had been noted previously in conditions causing hypopotassemia.

Bellet et al made extensive studies on 79 patients with hypopotassemia, one of whom had familial periodic paralysis, and confirmed the changes ascribed to hypopotassemia by Holler and other workers. There was no pathognomonic pattern; five electrocardiographic patterns were observed. The changes were predominantly in the T waves, S-T segments, Q-T intervals, and U waves The five patterns of S-T and T-wave changes associated with Q-T–segment prolongation consisted of the following: (1) depression of the S-T segments in varying degrees; (2) inversion of the T waves, (3) T waves of normal amplitude; (4) T waves of low amplitude; and (5) prominent U waves following the T waves. Eighty per cent of the records fell in the first two groups The electrocardiographic changes were immediately reversible following administration of potassium. The U wave was present in 42 per cent of the cases studied

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Cardiovascular manifestations of endocrine and metabolic diseases

GROSS AND MICROSCOPIC CHANGES OF THE HEART AND VESSELS IN DISEASES OF THE ENDOCRINE SYSTEM

THYROID GLAND

Hyperthyroidism. Tachycardia, increased cardiac output and blood velocity, and widened pulse pressure are common features of hyperthyroidism; they are related to the higher demand for blood created by the increased metabolic requirements. In thyrotoxicosis, cardiac activity is particularly exaggerated by exertion and excitement. It seems certain that the increased activity of the heart is due, at least in part, to a direct effect of the thyroid hormone on the myocardium. It has been shown that thyroxin forces the metabolism of muscle into aerobic channels, requiring greater direct consumption of oxygen. As a result of this, cardiac and skeletal muscles contain decreased amounts of glycogen (Menne et al.) and probably are depleted of other chemical stores In hyperthyroidism, cardiac muscle appears to be more sensitive to certain stimuli. For example, the sensitivity of cardiac muscle to epinephrine and other vasoactive drugs is increased in animals treated with thyroxin (Hoffman et al.). Atrial fibrillation is common and has been attributed to increased excitability of the atrial musculature.

Cardiac failure in the young, and otherwise healthy, hyperthyroid patient is not common, in spite of the exorbitant demands upon the heart. Myocardial insufficiency will develop more frequently in older patients, especially when the disease is protracted and the cardiac reserve has already been diminished by other diseases These numerous physiological and clinical manifestations of hyperthyroidism should theoretically be accompanied by important morphologic changes in the heart.

Post-mortem studies of the heart in hyperthyroidism and thyrotoxicosis are made difficult by superimposed complicating illnesses, agonal and post-mortem changes, and the effects of therapy. Older studies pointed to a variety of lesions. These include: hypertrophy

and dilatation, focal myocardial necroses, small scars and interstitial fibrosis, lymphocytic infiltration, true myocarditis, and fatty degeneration Weller et al studied the hearts of 35 patients who had had exophthalmic goiter. They failed to observe any gross or microscopic pathological change which was not equally represented in a carefully matched control series There was, however, a relatively higher incidence of myocardial fibrosis, endocardial sclerosis, and cellular infiltration Hypertrophy of the myocardium, fatty ingrowth, fatty degeneration, and arteriosclerosis were common in this series but not more frequent than in the controls In a large series of nodular nontoxic goiter, these workers failed to observe any differences from the controls

Friedberg and Sohval also found no characteristic changes in 27 hearts of patients with *Graves' disease* Hypertrophy was present in more than 50 per cent of the cases but could be explained on the basis of hypertension, coronary *sclerosis*, *atrial fibrillation*, and congestive heart failure *Numerous other studies* confirm the presence of cardiac hypertrophy in approximately 50 per cent of *the cases. It* is of interest that thyroid hormone has been found to sensitize the heart muscle to growth hormone and that the latter is *essential for* the development of cardiac hypertrophy (Beznak and Hajdu) However, according to Friedberg, the cardiac hypertrophy is minimal or absent in uncomplicated cases of Graves' disease, probably *because* of the normal stroke output and diastolic tension It is of interest that the incidence of myocardial infarction *in* thyrotoxicosis is low and that an *increase is* noted when the thyroid state is restored to normal (Jeffers et al.) Injections of thyroxin *into* rabbits and guinea pigs failed to induce specific changes in the myocardium (Menne et al, Rake and Mc Eachern, Andrus). The depletion of glycogen in and fatty degeneration of the myocardial fibers, early interstitial fibrosis, and mild histiocytic *infiltration* observed in these animals, were attributed to the excessive work load thrown *upon* the heart rather than to a direct effect *of thyroxin*

In hyperthyroidism, the plasma total cholesterol (C) is generally somewhat decreased and so is the plasma lipid phosphorus (P). The C/P ratio remains *within* the normal range (Gertler) Other studies have shown that there is an inverse correlation between the basal metabolic rate and serum protein–bound iodine concentration, on the one hand, and the clinically demonstrable incidence of aortic and peripheral arteriosclerosis, on the other. However, no definite relationship was observed between the serum cholesterol concentration and medial arteriosclerosis (Kirk et al).

Experimentally, it has been shown that the thyroid hormone, iodides, and thiocyanates are inhibitors of atherogenesis The mechanism (or mechanisms) by which these substances act is poorly understood but apparently it is not necessarily *through a reduction in* blood cholesterol In this respect, it is of interest that thyrotropic hormone *lowers blood cholesterol* but enhances cholesterol-induced *atherogenesis* (Katz and Stamler).

In conclusion, hyperthyroidism will often induce cardiac *hypertrophy through* overwork and, less commonly, other nonspecific changes of the myocardium, apparently as a result of hypoxia (Raab, 1953). There is no definite evidence that hyperthyroidism might decrease *the severity* of atherosclerosis

Hypothyroidism. The so-called *myxedema heart* was first recognized clinically by Zondek (1918). *Among* the features associated with *this* condition are enlargement of the heart, *slow pulse* rate with normal or low blood pressure, *distant heart* sounds, and electrocardiographic changes, particularly a tendency to low voltage.

Other abnormalities observed in *myxedema* are reduction of cardiac output, prolongation *of* circulation time, and reduction in plasma *and blood volumes (Andrus; Morris and* Blumgart). With specific therapy, the heart *size is* reduced and the electrocardiogram *returns to normal* It seems likely, however, that in *myxedema* both reversible and irreversible cardiac changes may develop, since in some instances *thyroid* therapy failed to modify the cardiac manifestations (*Holzmann*).

The anatomic changes of the heart in myxedema, although *studied* by many investigators, are still a subject of debate Older studies (1888) reported the heart to be *hypertrophied, flabby*, and dilated, microscopically, the *presence of swollen*, abundant interstitial connective *tissue with* a great excess of mucin was noted Dilatation of the heart and degenerative changes *in the* myocardium, char-

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Of particular interest are the previously mentioned changes (described first by Kountz and Hempelmann) in the ascending and abdominal portions of the aorta. This lesion consists of an accumulation of amorphous metachromatic basophilic material between the muscular and elastic fibers of the media, and is not associated with an inflammatory reaction In some cases, it was followed by *dissection and rupture of the aorta* The degree of the lesion is proportional to the duration of athyroidism.

Recently, an irregular thickening of the capillary walls in the myocardium was observed in cases of myxedema This change, however, has no correlation with either the duration of myxedema or treatment with thyroid hormone, and a similar thickening was also observed in instances of hypertension and inflammation (Baker and Hamilton). It is not clear whether this morphologic change is related to the markedly increased capillary permeability of myxedema (Lange).

The occurrence of *pericardial effusion* in myxedema has been observed both clinically and at autopsy, even in the absence of cardiac failure (Gordon, Feasby, Lerman et al ; Kern et al) It has also been reported as a development in thyroidectomized rabbits (Webster and Cooke) but not in those with myxedema induced by I^{131} (Kurland et al). This effusion has been found to contain cholesterol in a concentration of not over 20 per cent of the amounts present in the blood

ANTERIOR PITUITARY GLAND

Hyperpituitarism; Acromegaly Cardiac hypertrophy, involving especially the left ventricular myocardium, is a common feature of acromegaly in association with generalized splanchnomegaly (Courville and Mason). The weight of the heart may range from 500 to 1,300 Gm (Humphrey and Dixon, Cushing and Davidoff, Hejtmancik et al , 1951). There is some dispute as to whether there is an increase in the number or in the size of individual myocardial fibers. According to some authors, cardiac enlargement in gigantism is proportional to general body growth, but is far above the expected weight in acromegaly (Levene and Miller). Coronary atherosclerosis is common and is frequently associated with myocardial infarcts, fibrosis, and calcification. Dilatation of the blood vessels, and especially of the aorta, has also been mentioned.

Various factors have been suggested to explain these pathological findings. Hypertension is frequently found in acromegalic patients (Bartelheimer) and at times can be extremely severe (Zondek, 1920). It has been attributed by some to a concomitant hyperfunction of the basophil cells of the anterior pituitary gland but convincing evidence for this is lacking. The frequently associated hyperthyroidism and heart failure have also been held responsible, but the degree of cardiac hypertrophy is usually greater than might be expected from these causes alone. Diabetes mellitus is probably responsible in part for the severe degree and early appearance of atherosclerosis. It is apparent that the most important factor responsible for cardiac hypertrophy, in addition to hypertension, is the excessive production of growth hormone. Some experimental evidence strongly supports this view (Selye; Raab). As far as the other myocardial changes are concerned, these must be attributed to coronary insufficiency caused by atherosclerosis and the disproportion between myocardial mass and coronary flow.

Hypopituitarism; Simmonds' Disease. The main findings in the cardiovascular system in autopsies of patients with hypopituitarism are (1) *brown atrophy of the heart,* which is observed in about one-third of the cases; and (2) absence of a significant degree of arteriosclerosis (Ruggieri). This is in sharp contrast with the findings in hyperpituitarism where hypertrophy of the heart and severe arteriosclerosis are the rule

In extreme hypopituitarism, the heart may show changes similar to those found in myxedema (Cluxton et al); these consist of vacuolar degeneration of muscular fibers with basophilic degeneration of the cytoplasm and interstitial fibrosis (Dailey et al.).

THE ADRENAL GLAND

Hypercorticism; Cushing's Syndrome. The association of increased blood volume, hypertension, polycythemia, hypercholesterolemia, and diabetes mellitus, are some of the important features of Cushing's disease that might enhance the development of cardiovascular lesions.

The heart is generally hypertrophied, and

acterized by (1) loss of transverse striations, (2) granular disintegration, and (3) cloudy swelling of muscle fibers, were also observed. Schultz ascribed a peculiar infiltration of mucoid substance and a thickening or swelling of the aortic valve to the same cause. This interstitial material was homogeneous and stained bluish with hematoxylin, but differed in its staining properties from the myxedematous infiltration of the skin. Fishberg (1924) pointed out the frequency of coronary arteriosclerosis, small myocardial scars, and hypertension. All these factors may lead to myocardial insufficiency and, therefore, play an indirect role in the pathogenesis of heart failure in myxedema. Higgins mentioned that only five autopsy records at the Massachusetts General Hospital in Boston indicated myocardial changes of the heart in myxedema. In four of them, the changes consisted of interstitial edema and fibrosis; in the fifth, of fibrosis only. He believed that a *mucoid infiltration* of the myocardium appears early in myxedema, and that this is followed by further degenerative changes, coronary sclerosis, and interstitial fibrosis La Due (1943) observed marked hydropic degeneration of the sarcoplasm of the muscle fibers. Edematous material was also present between the muscle fibers, especially beneath the endocardium White believes that the enlargement of the heart in myxedema is due in part to dilatation and in part to the "myxedematous" changes in the myocardium. Means states that the heart is grossly edematous, leading to a condition of pseudohypertrophy. Brewer studied the nature of the mucoid infiltration of the heart by histochemical methods He noted that this material is PAS [1]-positive but is more resistant to digestion by hyaluronidase than is similar material observed in other tissues Foster and Barr, and several other investigators, noted lesions of muscles (including the myocardium), characterized by degeneration of the central portion of the sarcoplasm with the production of vacuoles containing a basophilic and granular material. This material was thought to be "fibroblastic mucoid" and considered similar to that seen in idiopathic cystic necrosis of the aorta, and in the aortic lesions observed by Kountz and Hempelmann in cases of induced hypothyroidism. Fisher and Mulligan conducted a quantitative and correlative study between basophilic degeneration of the myocardium and atrophy of the thyroid gland. They found considerable more basophilia of the muscle fibers in patients with atrophy of the thyroid gland than in a miscellaneous group of control cases Means has emphasized that one must distinguish sharply between the pathologic findings in treated and untreated patients. Typical changes of myxedema are found in untreated cases only.

In experimental myxedema, Webster and Cooke observed changes similar to those described by Foster and Barr. Other investigators (Brooks and Larkin; Goldberg, 1927), however, failed to observe these changes. The severity and duration of hypothyroidism are probably important in this respect.

An early incidence of atherosclerosis, apparently because of hypercholesterolemia, has been noted in patients with myxedema However, the associated increase in phospholipids may compensate for the elevated serum cholesterol. Friedberg found little support for the theory that myxedema predisposes human beings to atherosclerosis, a concept which he thinks has developed from the experimental evidence that atherosclerosis can be produced and enhanced by thyroidectomy (Goldberg). It has been the experience of some pathologists (Milles), however, that, as a rule, women who had undergone a thyroidectomy many years before presented at autopsy a greater degree of atherosclerosis than other women of comparable age. It is interesting (Bruger and Rosenkrantz) that the incidence of hypometabolism in subjects 55 years of age or older is greater among those exhibiting clinically detectable arteriosclerosis than among those without arteriosclerotic manifestations On the other hand, it has been reported (Blumgart et al) that the incidence of atherosclerosis is not greater than normal in myxedematous patients and that, in the absence of hypertension and cardiac hypertrophy, it is of only moderate degree (Baker and Hamilton). In one clinic, approximately 25 per cent of the patients with myxedema also had hypertension; and probably this is the most important single factor in enhancing atherosclerosis (Hamilton and Greenwood).

[1] Periodic acid Schiff staining procedure for mucopolysaccharides.

in adults with pheochromocytomas (Cahill; Kremer, Hueper). In several cases, however, no significant vascular changes were detected at autopsy (Green; Palmer and Castleman).

It should be noted that protracted administration of epinephrine to experimental animals tends to induce necrotizing and calcifying lesions, especially in the media of small arteries. Atherosclerosis is not a common finding in these animals, unless a high-cholesterol diet is administered simultaneously (Anitschkov; de Suto Nagy and Waters). It would appear, however, that hypertension per se is the most important factor in the pathogenesis of the arteriosclerosis observed in patients with chromaffin tumors of adrenal glands

PARATHYROID

Hyperparathyroidism. The cardiovascular manifestations of hyperparathyroidism are represented by (1) a tendency toward hypertension, in most cases on the basis of secondary renal involvement, and (2) by electrocardiographic changes related to hypercalcemia. Morphologically, the only significant lesion observed in the heart is the presence of *areas of calcification* in the myocardium (Allbright and Reifenstein, 1948). Although calcification of arterial walls is common, arteriosclerosis does not appear to be an important complication, at least in primary hyperparathyroidism Similarly, the cardiac lesions are not functionally significant (Raab).

Hypoparathyroidism. No significant morphologic changes have been described in the cardiovascular system of patients with hypoparathyroidism *Precordial pain* and *sudden death,* which occasionally occur in patients with tetany, are attributed to hypocalcemia and to the increased sensitivity of the heart and arteries to epinephrine (Raab).

PANCREAS

Hyperinsulinism and Hypoglycemia. Cardiovascular signs and symptoms are a prominent feature of hypoglycemia, whether this is due to islet-cell adenoma of the pancreas, insulin overdosage in the treatment of diabetes mellitus, or (insulin) shock treatment of schizophrenia Reduction in blood sugar may induce or aggravate hypoxia of the myocardium and precipitate attacks of precordial pain and myocardial infarcts. Some of these clinical features are attributed by some investigators to a compensatory secretion of epinephrine induced by hypoglycemia

Morphologically, no specific cardiac or vascular changes have been attributed to overproduction of insulin. However, in one case (observed by the author) of long-standing hypoglycemia caused by an islet-cell adenoma of the pancreas, death was caused by a *dissecting aneurysm of the aorta* Experimentally, administration of insulin and sugar to rats for periods up to 3 months induced glomerular and arteriolar changes of the diabetic type (Goth et al.).

Diabetes Mellitus. The association of diabetes with atherosclerosis and hypertension is well known. Coronary atherosclerosis, cardiac hypertrophy of moderate degree, and myocardial infarction are common findings at autopsy (Clawson and Bell). Control of diabetes mellitus by insulin, and the subsequent prolongation of the diabetic's life have greatly contributed to the increased severity of atherosclerosis in general and coronary atherosclerosis in particular. The predisposing effect of diabetes is further suggested by the fact that severe coronary atherosclerosis with occlusion is almost as common in diabetic women as in men (Bradley and Bryfogle). Further, coronary atherosclerosis of considerable severity is not uncommon among young diabetics. As a result, the incidence and severity of myocardial infarction are greater among diabetics Diabetic nephropathy, characterized morphologically by a peculiar form of capillary glomerulosclerosis and clinically (often) by the nephrotic syndrome, is an important factor in exacerbating the atherosclerotic lesions through the development of hypertension and of higher levels of serum cholesterol. The type of atherosclerosis observed in patients with diabetes mellitus does not differ from that seen in nondiabetics, except for the greater abundance of lipid deposits in the intima of elastic as well as muscular arteries, and for the frequency and severity of hyaline changes in the arterioles (Warren and LeCompte). No detectable morphological myocardial changes have been reported in association with the abnormalities of severe potassium concentration which occur in diabetic acidosis and its subsequent treatment with insulin (Henderson).

coronary atherosclerosis is severe. These changes are particularly prominent when hypertension is pronounced and is associated with diabetes mellitus (MacMahon et al.; Russell et al.; Ruggieri; Oppenheimer and Silver). Atherosclerosis of both large and medium-sized arteries has been observed, even in young adults and children with this syndrome (Raab, 1953). Heavy and prolonged treatment with cortisone and similar compounds with resulting Cushing's syndrome may induce similar vascular changes.

The possibility exists that the particularly severe form of atherosclerosis and hypercholesterolemia, usually present in patients with Cushing's syndrome (Hueper, 1935; Williams, 1951), may be related to a direct effect of cortisone on plasma lipids (Adlersberg et al., 1951) rather than to the coexistent diabetes mellitus.

There are no definite observations to indicate that androgen administration predisposes to or aggravates experimentally induced atherosclerosis. However, there are many studies indicating a prophylactic and therapeutic inhibition of coronary atherosclerosis by estrogens (Katz et al.). Masculinization and virilism, on one hand, and severe atherosclerosis, on the other, in Cushing's disease emphasize once more the male predisposition for atherosclerosis and the probable importance of sex hormones in this respect.

The few reported cases of *primary aldosteronism* (Conn and Louis) would appear to be associated with cardiac hypertrophy and severe arteriosclerosis.

Hypocorticism; Addison's Disease. The most common post-mortem findings in cases of untreated Addison's disease are (1) the reduction in size of the heart to well below the average normal size and (2) its brown color, i.e., *brown atrophy of the heart* (Addison; Barker; Guttman, Rowntree and Snell). Microscopically, except for atrophy and pigmentation by lipofuscin of the myocardial fibers, no changes of note have been observed in untreated cases (Sorkin).

Following the introduction of desoxycorticosterone acetate in the therapy of Addison's disease, several reports emphasized the presence in the myocardium of *small foci of necrosis* of myocardial fibers, often, but not always, accompanied by infiltration of lymphocytes (Goodof and McBride; Soffer; Sorkin, Sommerville et al.).

The reduction in the size of the heart in Addison's disease is generally attributed to the reduction in blood volume and associated hypotension (Friedberg, 1956). However, the importance of the loss of potassium and water from the myocardium, as well as from other muscular tissue (Zwemer and Truszkowski), cannot be disregarded. In addition, it is known that potassium is important for tissue-protein synthesis. Some of these myocardial changes may be due to the toxic action of sodium ions on cells that have lost a critical amount of potassium (Cannon et al.).

When desoxycorticosterone acetate and sodium are administered in large doses to patients with Addison's disease, sodium and water are retained, with simultaneous excretion of potassium and reduction in serum potassium levels. As a result, both blood volume and pressure are restored to normal or above normal levels, with an increase in size of the heart (Mc Gavack, Currens and White). The rapid loss of potassium from the blood will lead to depletion of the intracellular potassium of the myocardial fibers. The microscopic lesions found in the hearts of these patients are comparable to those produced in rats by the administration of desoxycorticosterone (Darrow and Miller) and by potassium-deficient diets (Follis, 1942; French). Similar changes, namely small areas of myocardial fibrosis and necrosis, have also been observed in patients with a history of hypokalemia due to different causes (Schwartz et al., 1954).

Hyperfunction of the Adrenal Medulla; Pheochromocytoma. Well-differentiated tumors of the adrenal medulla (of the pheochromocytoma type) produce excessive amounts of norepinephrine and epinephrine, with resultant paroxysmal or sustained hypertension. Cardiac enlargement and vascular changes may develop as a consequence. The hypertrophy of the heart predominantly involves the left ventricular myocardium, especially in patients with chronic hypertension (Green; Raab). The reactive capacity of the myocardium to epinephrine probably contributes to the development of cardiac hypertrophy (Raab). Small foci of myocardial fibrosis have been reported (Rothermich). Arteriosclerosis and atherosclerosis are common and fairly severe, especially

involved, with resultant stenosis. The *stenosis of the pulmonic valve* may be of considerable degree, with reduction of the circumference to as much as half of the normal size. The *tricuspid valve is often insufficient, as well as stenotic*. Histologically, the thick endocardium consists of coarse, often hyalinized collagen fibers. The splitting of elastic fibers in the endocardium and vascularization of the fibrotic valves without infiltration of inflammatory cells have also been described Thickening and fusion of chordae tendineae are common. Moderate hypertrophy of the right ventricular myocardium is usually present. Arterial lesions, which can be attributed directly to the effect of serotonin, have not been described (Thorson, Sjoerdsma et al; Isler and Hedinger, Bean et al.). Patients with carcinoid tumors have also been reported to present a higher incidence (33 per cent) of cardiovascular abnormalities than that (9 per cent) observed in a large series of autopsies (Spain).

The pathogenesis of the cardiac lesions is obscure. It would appear certain, however, that serotonin is directly involved Serotonin is normally destroyed in the liver. In the presence of carcinoid metastases to the liver, the blood originating from this organ would have an abnormally high concentration of serotonin when it reaches the right cardiac chambers. No endocardial changes are seen in the left cardiac chambers, where the blood contains little or no serotonin, unless there is a shunt, such as patent foramen ovale. The possibility that these patients might also be relatively deficient in tryptophan, from which serotonin derives, has also been mentioned as a factor involved in the pathogenesis of muscle wasting and skin changes observed in the carcinoid syndrome (Sjoerdsma et al.).

CLINICAL ASPECTS OF CARDIOVASCULAR DISTURBANCES IN ENDOCRINE DISORDERS

The cardiovascular complications which occur in several endocrine syndromes, aside from commanding considerable clinical interest, have a broad significance as valuable guides to a better understanding of many cardiovascular disorders in which more subtle and inconspicuous endocrine mechanisms are at fault

PHEOCHROMOCYTOMA

Catecholamine-discharging tumors of the adrenal medulla or of other parts of the sympathetic nervous system (paragangliomas) represent Nature's most instructive "experiment." They demonstrate the importance of exaggerated catecholamine action, either paroxysmal or sustained, on cardiovascular function and structure The complete and rapid curative effect achieved by timely removal of such tumors adds greatly to the conclusiveness of a reasoning which attributes to the catecholamines an outstanding pathogenetic role in many common diseases of the cardiovascular system. Patients harboring a pheochromocytoma share with an infinitely larger number of individuals such pathological manifestations as a labile or fixed systolic and diastolic hypertension, cardiac hypertrophy, attacks of precordial pain and pulmonary edema, cardiac arrhythmias, renal insufficiency, lesions of the retinal vessels and, in some instances, a high basal metabolic rate. All these phenomena are reversible by early excision of a pheochromocytoma but, in most instances of general sympathetic overactivity ("essential hypertension," "hypertensive" heart disease, etc.), they can be only partially relieved by surgical or medical measures directed against the operative sympathetic nervous system.

The most dramatic and most pathognomonic clinical signs of pheochromocytoma are *hypertensive paroxysms* According to a prevalence of either norepinephrine or epinephrine, there is (besides high systolic pressure elevations) either a rise or fall of the diastolic pressure, and either slowing or acceleration of the heart rate The paroxysms last from minutes to hours and may be accompanied by headache, anxiety, precordial pain, pallor, tremor, paresthesias, nausea, rise of temperature, and cardiac arrhythmias (such as extrasystoles, atrial fibrillation and AV conduction disturbances). A "hypoxic" pattern of the electrocardiogram (depressed T and S-T pattern) may persist for days after an attack. Pulmonary edema and fatal ventricular fibrillation or arrest may ter-

GONADS

The severity of coronary atherosclerosis and the incidence of coronary thrombosis are considerably greater in males than in females, especially before the menopause. This is particularly true when there are no complicating factors, such as hypertension or diabetes mellitus. After the menopause, the incidence of coronary atherosclerosis and myocardial infarction rises considerably in women although it is still lower than in man. Surgically induced menopause would also seem to accelerate the development of atherosclerosis (Wuest et al.). The predilection of the male sex for atherosclerosis is explained on the basis of differences in lipid metabolism between the two sexes and on the preventive effect of estrogen on the development of atherosclerosis; the latter view is also supported by numerous experimental observations (Katz et al).

On the other hand, masculinizing tumors of the ovaries are not commonly associated with distinctly greater severity of coronary atherosclerosis. The same is true of the adrenogenital syndrome, unless Cushing's syndrome is also present.

THYMUS

The function of the thymus is unknown and it is not certain that this organ should be classified as one of the endocrine glands However, a close relationship exists between the thymus and many endocrine glands It is known that thymic tumors may be associated with cardiovascular manifestations. Association of *thymic tumors* (or thymomas) with the complete Cushing syndrome, including hypertension, has been described (Leyton et al.) More commonly, thymic tumors are associated with *myasthenia gravis.* Myocardial changes have been observed in many cases of myasthenia gravis and were more severe in the presence of thymoma (Mendelow and Jenkins). They consisted of focal atrophy and vacuolization of the myofibrils with lymphocytic infiltration and occasionally of focal myocardial necroses These changes are not consistently found, and there are many cases of myasthenia gravis where no morphologic changes of note are observed in the myocardium.

Most authors do not recognize the existence of the so-called *status thymico-lymphaticus,* not, in any case, as a morphologic pathologic entity (Greenwood and Woods, Young and Turnbull). Certainly, the pressure of the enlarged thymus on the trachea is a factor of no importance.

However, according to some investigators (Marine; Symmers, 1934), this syndrome of generalized lymphoid hyperplasia does exist and is associated with hypoplasia of the vascular system and of the adrenal glands Sudden death in these patients would be attributed to adrenocortical insufficiency. Clinical and experimental observations on the role of adrenocortical hormones in the destruction of lymphoid tissue certainly suggests a close relationship between adrenal glands and the thymus.

THE CARCINOID SYNDROME AND HYPERSEROTONINEMIA

Thorson and his coworkers have described a clinical syndrome characterized by attacks of atypical bronchial asthma, cyanosis, flushing and telangiectasis of the skin, diarrhea, and right heart failure with anasarca, in association with carcinoid tumor of the intestine accompanied by metastases to the liver. This type of tumor had been previously found to contain large amounts of 5-hydroxytryptamine This substance was determined to be chemically identical with enteramine and serotonin (Erspamer and Asero). Serotonin is produced, not only by carcinoid tumors but also by the enterochromaffin cells from which these tumors derive and which are normally found in the mucosa of the intestinal tract. Serotonin directly affects the smooth musculature of blood vessels, bronchi, and intestine. It can be classified as a hormone because of its widespread action on the body and because the cells from which it originates fulfil the definition of endocrine. In this respect, it is interesting that, in the original description, carcinoid tumors were referred to as endocrine tumors.

The pathologic cardiac changes in patients with the carcinoid syndrome predominantly involve the endocardium of the right ventricle and are of considerable interest. They consist essentially of either diffuse or patchy *endocardial thickening and fibrosis.* The tricuspid and particularly the pulmonic valves are also

Primary aldosteronism, first described by Conn, is a syndrome, caused by the exclusive overproduction of aldosterone, usually from a tumor of the adrenal cortex It is characterized by muscular weakness, paresthesias, polyuria, polydipsia, hypokalemia and hypernatremia, arterial hypertension, and renal arteriolosclerosis, but no edema.

When the diagnosis of hyperadrenocorticism or primary aldosteronism has been definitely established, surgical exploration is indicated in order to rule out malignancy, to remove a neoplasm if one is found, and, in the absence of a tumor or of cortical hyperplasia, to perform subtotal adrenalectomy The latter offers the best guarantee for a more or less complete normalization Pre- and postoperative managements require considerable skill and resemble those mentioned in connection with the excision of pheochromocytomas. Roentgen-ray irradiation or electrical coagulation of the anterior pituitary are sometimes successful but do not eliminate the dangers of recurrence or of a malignancy remaining unrecognized.

HYPOADRENOCORTICISM (ADDISON'S DISEASE, POSTADRENALECTOMY SYNDROME, HYPOPITUITARISM-INDUCED HYPOADRENOCORTICISM)

The clinical signs of prolonged and severe deficiency of adrenocortical function (muscular weakness, pigmentation, anorexia, gastrointestinal symptoms, tendency toward "crises" under stress) have been known for a long time

In cases of general hypopituitarism, the signs of secondary adrenocortical hypofunction merge with those of other secondary endocrine deficiencies (hypogonadism, hypothyroidism) and are usually less severe Hyperpigmentation is minimal or absent.

The cardiovascular complications of hypoadrenocorticism are the reverse of those seen in Cushing's syndrome, and are essentially attributable to the reverse pattern of electrolyte disturbance, namely to a loss of sodium, and consequently to a diminution of vascular sensitivity to the pressor catecholamines of the vascular walls The blood pressure falls below the normal level or, in formerly hypertensive individuals, to near normal values Orthostatic hypotensive episodes occur readily. *The size of the heart is subnormal* (roentgenographic cardiothoracic ratio of 0 40 or less). Heart action is weak but congestive heart failure never occurs. Electrocardiographic changes, if any, consist chiefly of *low voltage*, prolonged P-R and Q-T, and flat or inverted T waves Critical situations arise during stress-induced acute exacerbations, when dehydration, fever, azotemia, hypovolemia, and loss of vascular tonus and reactivity produce a shocklike syndrome which, if untreated, almost inevitably ends in death

The *diagnosis* of adrenocortical insufficiency is based, aside from the above-mentioned clinical features, on the findings of a low blood-sugar level and glucose tolerance curve, hyponatremia and hyperpotassemia; a positive water test (Robinson et al); decreased excretion of corticoids in the urine; and the failure of ACTH to provoke eosinopenia within 4 hr or an increase of urinary 17-ketosteroid excretion within 8 hr (Jenkins et al.).

The *maintenance treatment* of adrenocortical insufficiency requires the lifelong administration of cortisone or hydrocortisone (with or without added desoxycorticosterone acetate) by parenteral or oral route, and extra amounts of sodium chloride (Hills et al). Desoxycorticosterone acetate and sodium chloride are particularly effective in restoring the cardiovascular status to normal but require meticulous supervision because hypertensive elevations of the blood pressure and congestive heart failure with pulmonary edema may be provoked by even a moderate overdosage. Stressful situations require an increase in the cortisone dosage. During the hot season, an additional intake of sodium chloride and desoxycorticosterone is advisable. In cases of crisis, the cortisone dosage must be greatly increased in combination with the intravenous administration of fluids, glucose, and sodium.

Withdrawal of corticoid therapy is sometimes feasible in subtotally adrenalectomized patients, but it should be accompanied and followed for a few days by administration of ACTH to compensate for the inhibitory effect which preceding corticoid administration had exerted upon the pituitary and thus, indirectly, on the functional reserve of whatever cortical tissue may still be present.

PREGNANCY

In normal pregnancy, the circulatory volume is markedly increased through the ninth month.

minate the clinical course. Transient states of renal excretory insufficiency, sometimes progressing to full-fledged uremia, occur even in otherwise asymptomatic cases of pheochromocytoma or in connection with hypertensive paroxysms.

In the earlier stages, the intervals between attacks are often entirely symptomless. Under such circumstances, the diagnosis can be made (aside from pyelogram and perirenal air insufflation) by eliciting a typical attack through the rapid intravenous injection of *histamine* (0.025 to 0.05 mg). The injection should be immediately followed by a rise in the blood pressure to a higher peak than that produced by the cold pressor test (immersion of a lower arm in iced water for 60 sec), but false positive responses may occur. Occasionally, *deep manual massage of the adrenal area* can provoke an attack and reveal the site of the tumor's location.

The sustained type of pheochromocytoma-induced hypertension, developing either insidiously, or gradually between paroxysms, is superficially indistinguishable from ordinary essential hypertension but can be identified by an assay of plasma and urine for augmented catecholamines (Manger et al.; von Euler and Ström) and by a positive response to adrenolytic agents. For example, the intravenous injection of 5 mg of *Regitine* causes a rapid fall of the blood pressure, exceeding 35 mm systolic and 25 mm diastolic. *Benzodioxane* can also be used but may cause an alarming blood-pressure rise in cases of essential hypertension

Atheromatous and arteriolosclerotic vascular lesions with particular involvement of the renal arterioles were commonly found in the past in untreated cases of pheochromocytoma, even in young children. *Cardiac hypertrophy* is frequently seen in both the sustained and the paroxysmal hypertensive syndrome of pheochromocytoma *Coronary atherosclerosis,* although encountered at as early an age as 10 years, is not a regular complication of pheochromocytoma, but degenerative and fibrotic foci not infrequently appear in the heart muscle.

The only decisively effective treatment for pheochromocytoma is *early excision* of the tumor or tumors. Pre- and postoperative administration of dibenamine, Regitine, norepinephrine, and cortisone is necessary to combat the hazards of both excessive blood pressure rises and falls, respectively, which are connected with the surgical procedure. Dibenamine and Regitine also prove useful in giving symptomatic relief from paroxysms as long as the tumor is still in place.

HYPERADRENOCORTICISM

Cushing's Syndrome; Primary Aldosteronism. An overproduction of adrenal sodium-retaining mineralocorticoids, which cause cardiovascular complications, occurs in the presence of adrenocortical tumors (benign or malignant) or of cortical hyperplasia. It also not infrequently occurs without any recognizable changes in the adrenal cortex. Coexistence with a basophilic adenoma of the anterior lobe of the pituitary (Cushing's disease) is not uncommon

Depending upon the types and combinations of corticoids which are produced in excess (mineralocorticoids, glucocorticoids, or androgens), the clinical picture will assume a variety of appearances. Exclusive overproduction of glucocorticoids or androgens, or both, may leave the cardiovascular system unaffected and give rise only to the metabolic features of Cushing's syndrome (trunk obesity, diabetes, striae, osteoporosis) or of the "adrenogenital" syndrome (masculinization). Simultaneous mineralocorticoid overactivity, on the other hand, often causes a very high and stable elevation of the systolic and diastolic blood pressures, even in young children; early development of arteriosclerotic and atheromatous vascular lesions, especially in the kidneys, cardiac hypertrophy; and ultimate progression to congestive heart failure. The electrocardiogram shows, as a rule, the characteristics of "hypertensive" heart disease (left ventricular strain pattern). All in all, the cardiovascular syndrome of hyperadrenocorticism can be diagnosed only by the evidence of somatic glucocorticoid and androgen overactivity and by certain laboratory findings: diminution of sodium in the thermal sweat and saliva, and low serum-potassium values, paralleled by an increased urinary excretion of mineralocorticoids. Because of the technical difficulty and costliness of corticoid determinations, the assay *of 17-ketosteroids in the urine* is frequently used as an indirect, and not always sufficiently informative, criterion of hyperadrenocorticism.

In the nonprogressive phase of the disease, which may extend over many years, it is preferable, however, to administer a merely symptomatic treatment of the cardiac complications.

DIABETES MELLITUS

No specific cardiovascular derangements are attributable to the diabetic state per se, but diabetic individuals exhibit a predisposition to the premature development of arterial hypertension and of atherosclerosis in the heart, extremities, kidneys, and brain

Clinical signs of *coronary sclerosis* are common. They appear (on an average) 9 years after the onset of diabetes. The sex difference in the incidence of coronary heart disease (ordinarily male : female = 4 1) is abolished among diabetics. The *statistical* occurrence of myocardial infarctions and congestive heart failure is higher in diabetic than in nondiabetic individuals. *General arteriosclerosis* in diabetics is distinguished by its severity and early appearance Involvement of the arteries of the legs is said to occur eleven times more frequently in diabetics, while qualitatively the lesions are similar to those of nondiabetics The vascular changes which constitute the clinical picture of "diabetic retinitis" resemble those of malignant hypertension

Treatment of the vascular and cardiac complications of diabetes is similar to the routine management of such conditions However, any overdosage of insulin should be carefully avoided in the presence of cardiac pathology because of the danger of resulting epinephrine discharges. Fat and cholesterol in the diet should be kept to a minimum

The cardiovascular situation in *diabetic acidosis* and *coma* is similar to that in shock, as it progresses into the third, "decompensatory" phase Besides the energetic use of insulin, it should be treated with intravenous infusions of saline or sodium lactate solutions Infusion of norepinephrine is to be recommended when blood pressure has fallen to a critically low level. In contrast to epinephrine, norepinephrine does not interfere with carbohydrate metabolism. Following successful insulin treatment, it is important to watch for signs of hypopotassemia and to combat it through an adequate administration of potassium.

HYPERINSULINISM

"Absolute" hyperinsulinism is caused by the discharge of abnormally large amounts of insulin from benign or malignant tumors of the islets of Langerhans or from their metastases. It manifests itself in the form of attacks of pallor, trembling, perspiration, paresthesias, palpitations, epigastric pain, nausea, ravenous hunger, weakness, and eventual prostration and convulsions, sometimes ending in death. These severe hypoglycemic attacks may be elicited by strenuous exercise or by fasting, or they occur a few hours after carbohydrate-rich meals They are caused jointly by the acute hypoglycemia and the secondary massive discharges of epinephrine from the adrenal medulla. Accordingly, there is an increase of systolic pressure, pulse pressure, heart rate, and cardiac output Depression of the S-T segment with flattening or inversion of the T waves, extrasystoles, atrial fibrillation, and precordial pain are observed, especially in elderly individuals. They correspond to the side effects elicited by insulin-shock therapy in mental patients. Milder symptoms of a similar kind have been noted in abnormally sensitive persons during the postprandial hypoglycemic phase

Unless the tumor can be removed surgically, it is necessary to avoid situations provoking hypoglycemia and to adhere to a low-carbohydrate, high-protein diet, with enough fat for caloric requirements, distributed in five or six small meals over the day. However, if an attack is under way, the immediate intake of sugar or intravenous infusion of glucose becomes imperative Patients afflicted with severe hyperinsulinism should always carry a tag with first-aid instructions

HYPERTHYROIDISM

The functional state of the thyroid gland *is governed* by the thyrotropic hormone of the pituitary. A primary exaggerated production of the *latter is* assumed to be responsible for some forms of hyper*thyroidism* Others are attributed to derangements of *cerebral* centers (emotional, encephalitic, carbon monoxide poisoning) which *are likely to* overstimulate the formation of thyrotropic hormone by *the* pituitary, or to the presence of an adenoma of the thyroid gland *In certain* iodine-poor

It returns toward normal at term. Cardiac output, stroke volume, and velocity of blood flow are likewise increased. The maximal development of all these phenomena coincides with the peak of total corticoid production between the 200th and 240th days of gestation. It also coincides with the highest statistical incidence of *congestive heart failure* in women with preexisting cardiac disease. Labor is usually relatively well tolerated by such patients, although some succumb to *shock* and *pulmonary edema* shortly post-partum.

The treatment of congestive heart failure in pregnancy is essentially the same as that outside of pregnancy. Even surgical interventions, such as mitral commissurotomy, have been successfully performed in selected cases.

Pharmacodynamic studies (Assali et al.) concerning an exaggerated depressor effect of tetraethylammonium bromide (TEAB) suggest a shift toward sympathetic neurogenic mechanisms in the maintenance of normal blood-pressure levels in pregnancy.

The *pretoxemic and toxemic complications* of pregnancy, such as sodium retention, edema, albuminuria, arterial hypertension, and eclampsia in the third trimester, are being increasingly recognized as the result of an *excessive production of mineralocorticoids* (Venning et al.). There are some indications that a part of these corticoids originates in the placenta. An abnormal pressor responsiveness to catecholamines, like that produced by desoxycorticosterone acetate administration, develops as an early feature of pretoxemia from about the thirtieth week on. It can be utilized as a prognostic criterion (Raab et al.) and calls for prophylactic and therapeutic measures, such as salt restriction and antihypertensive drugs.

MENOPAUSE AND HYPOGONADISM

Cardiovascular disturbances connected with the premenopausal and menopausal state are multiple, irregular, and generally not serious. *Flushing of the skin* on upper chest, neck and face, lability of the blood pressure with a tendency toward an increase, palpitation; dizziness; tachycardia; acrocyanosis; and Raynaud's phenomenon are common *Precordial pain*, with or without radiation into the left arm but independent of exertion and usually prolonged, is not infrequent. It is sometimes associated with transient "hypoxic" changes in the electrocardiogram.

Moderate *ankle edema, exertional dyspnea* and *sighing respiration* must not be mistaken as evidence of congestive failure. They may be explained as due to temporary overactivity of the adrenal cortex and of cardiorespiratory reflexes.

Treatment with estrogens (possibly combined with small doses of testosterone) is usually sufficient to suppress the most annoying symptoms. Roentgen-ray irradiation of the pituitary and of the adrenal glands has also been recommended. Barbiturates and rauwolfia derivatives are indicated for emotional instability and the accompanying fluctuations of the blood pressure.

Castration of both males and females is often followed by similar neurovegetative cardiac and circulatory manifestations, like those seen in the menopausal syndrome. They usually respond well to the substitutive administration of sex hormones.

ACROMEGALY AND GIGANTISM

Acromegaly, caused by eosinophilic tumors of the anterior pituitary lobe in the adult, and gigantism, its closely related equivalent beginning before puberty, are due to overproduction of the pituitary growth hormone and are often accompanied by slight over- or underfunction of the thyroid, as well as by mild adrenocortical overactivity.

One cardiac abnormality which seems to be rather specific for acromegaly (but less so for gigantism) is *enlargement of the heart*. It may greatly exceed the simultaneous increase in size of the other organs, and reach enormous proportions (up to 1,300 Gm), whether the blood pressure is elevated or not *Congestive heart failure* usually develops at the average age of 42 years and terminates the patient's life in a high percentage of cases. *Arterial hypertension* is less frequently observed and displays a labile, sometimes paroxysmal, character. General arteriosclerosis, renal arteriolar sclerosis, and degenerative alterations of the heart muscle are commonly found at autopsy.

Therapy consists of *surgical removal of the tumor*. Implantation of radon seeds and roentgen-ray irradiation are also used occasionally.

vision of the white blood count in order to avoid a possible dangerous agranulocytosis. They must be used continuously for *18 months* or longer to provide a lasting curative effect. Radioiodine therapy is easier to complete in a few sessions but may cause *irreversible myxedema if the dosage* is too high. Like all antithyroid forms of therapy, it is apt to *provoke hypercholesterolemia*, a potential long-range hazard to the coronary circulation

Digitalis ordinarily proves useful in patients with a rapid ventricular rate, provided that it is caused by atrial fibrillation, and is used in frank *congestive failure*.

HYPOTHYROIDISM

States of thyroid hypofunction may be artificially induced by thyroidectomy or antithyroid medication. *Primary hypothyroidism* develops relatively frequently in middle-aged women and, as a secondary feature, in cases of *hypopituitarism (pituitary myxedema)*, especially *in multiparous women* The incidence of hypothyroidism in men is one-tenth to one-fifth that prevalent among women. In cases of sporadic or endemic *cretinism*, a hypofunction of the thyroid appears as a side phenomenon in combination with severe primary cerebral deficiencies

The term *myxedema* refers to the accumulation of a protein-rich gelatinous *material in the subcutaneous tissues*. It must not be confused with the true "pitting" edema of congestive heart failure. It is associated with a puffy, pasty appearance of the dry, scaly skin, coarse, brittle hair; *constipation, oversensitivity* to cold temperatures; general fatigue; a hoarse, husky voice; *slow*, poorly articulated speech; and marked *mental apathy*.

Except in cases of "pituitary myxedema," the *blood cholesterol level is elevated*. Protein-bound iodine of the *serum is reduced*, and the uptake of radioiodine *by the thyroid gland* is diminished or entirely absent. A markedly *lowered basal metabolic rate* is consistent with the diagnosis of hypothyroidism, but moderate depressions (as much as −25 per cent) *may* also occur, unrelated *to thyroid underfunction* (Kurland et al.). The blood pressure level is *not characteristically affected* by the hypothyroid state The pulse pressure may be diminished Catecholamine activity is reduced to a minimum and, accordingly, heart action and peripheral blood flow are sluggish; the cardiac output is decreased A *low voltage of P, T, and QRS* represents the most specific electrocardiographic *feature of the "myxedema heart."* It is believed to be caused by short-circuiting and dissipation of the action currents within the swelled myocardium itself and within the other *myxedematous tissues* that connect the heart with the *registering electrodes*. Depression of the voltage becomes maximal in the presence of pericardial effusion. The latter *consists of fluid with a high* protein content. In many instances, it is responsible for an *enlargement of the heart silhouette* on roentgenography. This enlargement disappears *after the pericardial sac is tapped* (Fig 16-9).

Fig 16-9. Enlargement of the cardiac silhouette in myxedema caused by pericardial effusion Tapping of the pericardial sac reveals the true size of the heart (From Zdansky Roentgendiagnostik des Herzens und der grossen Gefasse, 1949.)

areas of the world (e.g., the European Alps), thyrotoxicosis due to excessive medicinal intake of inorganic iodine compounds or thyroid preparations, is widespread.

The *diagnosis* of hyperthyroidism rests upon (1) a well-known but variable clinical picture (diffuse or nodular enlargement of the thyroid gland, wide palpebral aperture without or with exophthalmos, moist flushed skin, dermographism, silky hair, fine tremors, psychomotor restlessness, loss of weight, oversensitivity to warm temperature); and (2) laboratory tests (evidence of increased basal metabolic rate and protein-bound iodine and a greater radioiodine uptake by the thyroid gland). The incidence of thyrotoxicosis is far greater in women than in men

The *cardiovascular manifestations* of hyperthyroidism are based upon an intensive potentiation of epinephrine and norepinephrine. Accordingly, they mimic the effects of these neurohormones cardiac acceleration, palpitation; increased stroke volume, cardiac output, and pulse pressure, augmented pulse-wave velocity; and increased peripheral blood flow There is a theory proposing that these phenomena take place "in order" to fulfill the oxygen demands of the peripheral tissues; however, this ignores the catecholamine-mediated influence of the thyroid hormone on the myocardium, a phenomenon which can be observed even on isolated hearts.

Paroxysmal and ultimately permanent *atrial fibrillation* occurs in untreated patients, especially in the more advanced age groups. This phenomenon, as well as an occasionally observed bradycardia, prolongation of the P-R interval, and an only moderate rise of myocardial oxygen uptake (Leight et al) suggests a simultaneous accentuation of cholinergic mechanisms

Preexisting "organic" heart disease is often greatly aggravated by thyrotoxicosis

Interesting analogies exist between the thyrotoxic and the beriberi heart, both of which are characterized by exaggerated catecholamine action: the former due to abnormal functional potentiation, the latter due to actual accumulation of catecholamines in the heart muscle. A relative thiamine deficiency is also believed to participate in the thyrotoxic cardiovascular syndrome.

Although the systolic blood pressure is sometimes moderately elevated in hyperthyroid patients, the diastolic pressure tends rather to fall (epinephrine effect). The frequently heard statement that thyrotoxicosis promotes essential hypertension is unfounded. A *slight enlargement of the heart silhouette* is sometimes noted on roentgenography and an unusual prominence of the conus of the right ventricle represents a characteristic peculiarity of the thyrotoxic heart. At autopsy, the heart muscle is often found to be hypertrophied, with disseminated degenerative and necrotic foci, similar to those experimentally produced by epinephrine.

Coronary atherosclerosis and myocardial infarctions are comparatively uncommon (Jeffers et al.), probably because of the anticholesterolemic effect of the thyroid hormone Accordingly, precordial pain does not occur as frequently as one might expect in view of the effects of the thyroid hormone in promoting precordial pain in patients with coronary sclerosis.

The electrocardiographic signs are nonspecific, except for the frequent occurrence of *high P and T waves*, which have been interpreted as a manifestation of exaggerated sympathetic tone. Depressions of S-T and T make their appearance in more advanced stages when myocardial hypoxia and degeneration become prominent.

The three main forms of *treatment* for hyperthyroidism and for its cardiac complications are· thyroidectomy; use of antithyroid drugs, such as propyl- and methylthiouracil or Tapazole; administration of radioactive iodine

Surgery has been partially replaced by the medical procedures, but it still remains the treatment of choice in most adenomatous cases as the best guarantee against later malignancy and in the presence of tracheal compression Iodine, alone or in combination with propylthiouracil, is used in the preoperative period to improve the patient's condition rapidly and to decrease the surgical risk. Atrial fibrillation may appear and persist for several days following thyroidectomy. The so-called "thyrotoxic crises," which are in rare instances elicited by the surgical trauma or by other stressful situations, are probably attributable to a secondary acute adrenocortical insufficiency and are to be treated accordingly.

Thiourea derivatives require constant super-

sudden death, especially among children with tetany, have been ascribed to an increased sensitivity of the cardiovascular system to epinephrine.

Therapy consists essentially of attempts to restore a normal blood calcium level by administration of parathyroid hormone, calcium gluconate, or dihydrotachysterol.

CIRCULATION TIME IN HYPERTHYROIDISM

Blumgart et al. (1931), with the aid of radium C, and Tarr et al., by the use of Decholin, have demonstrated that in hyperthyroidism there is a heightened velocity of blood flow and an abbreviated circulation time which are inversely proportional to the level of the basal metabolism

In hyperthyroidism uncomplicated by coexisting valvular or myocardial disease or by atrial fibrillation, the velocity of blood flow may be remarkably increased, varying with the level of the metabolism. The circulation times of both segments of the pulmonary pathway from the antecubital vein to the pulmonary capillaries ("arm-to-lung" time) and from the pulmonary capillaries to the capillaries of the tongue ("lung-to-tongue" time) are proportionately decreased. Thus, the "arm-to-lung" time with ether (Hitzig) may be within the range of from 3 to 4 sec, whereas the "arm-to-tongue" time with Decholin or saccharin or calcium may be reduced to levels of 7 to 10 sec in contrast to a normal value of 10 to 16 sec with the same methods

The augmented circulation time in hyperthyroidism increases about 30 to 70 per cent in order to balance an increased cardiac output, an increased venous return, and a slightly increased circulating blood volume. The increased circulation speed is a reflex response to the increased oxygen consumption of a heightened metabolism which compels increased demands of the tissues for more oxygen per unit of time This disturbance in the oxidative needs of the tissues leads to an accumulation of metabolites which causes reflex lowering of the peripheral resistance through the mechanism of vasodilatation and short-circuiting effects of newly opened and functioning arteriovenous shunts.

When hyperthyroidism complicated by coexisting heart disease ushers in congestive failure as a consequence of either atrial fibrillation or myocardial strain (both pathogenetically related to thyrotoxicosis), the circulation time may remain rapid or drop within normal limits depending upon the level of the metabolism and the degree of heart failure. Even in cases with a high initial *venous pressure* and a marked hepatojugular *reflux (characteristic* of congestive failure), *the circulation time* may still remain within the normal healthy range of from 10 to 16 sec or slightly higher (Hitzig). *The syndrome of congestive heart failure with a normal or* rapid circulation time (if anemia, beriberi heart, fever, acute pulmonary *insufficiency*, or arteriovenous fistula can be excluded) is pathognomonic of hyperthyroid*ism complicating* coexisting heart disease

HYPERTHYROIDISM VERSUS NEUROCIRCULATORY ASTHENIA

Circulation times offer a simple bedside tool for the clinician who is at times confronted with the problem of differentiating between hyperthyroidism and conditions which mimic it closely. The latter includes neurocirculatory asthenia and various forms of anxiety states, in which tachycardia is a prominent presenting symptom. Because of the hypermetabolism of Graves' disease, the cardiac output is *increased*. While the circulation time remains within *the normal* range in neurocirculatory asthenia, it is *frequently* abbreviated in hyperthyroidism, the "arm-to-tongue" time often being reduced to a range of 6 to 9 sec

THE FATTY HEART

Two types of fatty change occur in the heart (1) fatty degeneration and (2) fatty infiltration Fatty degeneration *is part of* a degenerative process, and the consensus is that it has *nothing in* common with "fatty heart." Fatty infiltration of *the myocardium*, lipomatosis cordis, or cor adiposum, *are* terms often used instead of "fatty heart"

Both the pseudoenlargement of the heart and the pseudoedema of the peripheral tissues in hypothyroidism have created considerable confusion as to whether *congestive failure* is a characteristic feature in myxedema. Absence of true congestive phenomena, unresponsiveness to digitalis, and improvement under thyroid medication, set the picture of "the myxedema heart," apart from that of congestive failure. It must be emphasized, however, that hypothyroidism may be associated with congestive heart failure in certain circumstances.

Severe *coronary atherosclerosis* is a common complication of hypothyroidism, presumably in connection with its concomitant high cholesterol levels. The not infrequent occurrence of *precordial pain* and *signs of congestion* can be explained on this basis. Accordingly, the usefulness of therapeutic thyroid depression in cases of angina pectoris and congestive failure with coronary sclerosis is limited, and the loss of thyroid function may ultimately aggravate such cases.

At autopsy, the hearts of persons who have died in untreated hypothyroidism appear pale, flabby, and sometimes dilated If an increase in the ventricular mass is seen, this is due to myxedematous swelling of the myocardial fibers rather than to hypertrophy As a result of the common presence of coronary atherosclerosis, fibrotic changes are often noted.

The specific *treatment* for hypothyroidism consists of the administration of *thyroid hormone* (U.S P dry powder preparations) or of the more rapidly acting *triiodothyronine* (Zondek et al). Since patients with "pituitary myxedema" are extremely sensitive to the stress-producing effects of thyroid medication and may succumb to it in a state of hypoadrenocortical crisis, it is mandatory to administer the thyroid hormone to such patients only in minimal doses, and to combine it with *cortisone, ACTH, or both* Thyrotropic hormone of the anterior pituitary may be used instead of thyroid preparations (De Gennes).

Great caution is necessary in patients over fifty and in those with a history of coronary or hypertensive heart disease Severe precordial pain or heart failure may be precipitated by thyroid preparations through their potentiation of catecholamines It is preferable to increase the medication slowly over several months until a maintenance dosage is obtained, rather than to take risks through hasty overtreatment. Morphine and barbiturates are contraindicated in hypothyroid patients.

HYPERPARATHYROIDISM

The result of excessive hormone production by adenomas of the parathyroid glands is revealed in disturbances in the metabolism of calcium and phosphorus. Calcium is mobilized from the bones, thus giving rise to widespread decalcification of the skeleton, partly in cyst-shaped areas, and especially in the long bones. Some of the calcium is eliminated with the urine, while excess amounts accumulate as kidney and urinary stones or are absorbed by soft tissues, including the vascular walls and the myocardium. The diagnosis is based on the typical radiological findings, a high level of ionized calcium and of alkaline phosphatase, and a low concentration of inorganic phosphorus in the blood. *Abbreviation of the electrical systole, with a shorter Q-T interval,* is frequently seen in such cases. Renal lesions may contribute to the development of nephrogenic arterial hypertension. Caution in the use of digitalis glycosides has been recommended in view of a possible exaggeration of digitalis toxicity by the hypercalcemia.

HYPOPARATHYROIDISM

This condition affects the metabolism of calcium and phosphorus in a sense opposite to that prevailing in hyperparathyroidism. It lowers the level of ionized calcium in the blood and usually reverses the calcium/phosphorus ratio It occurs following spontaneous lesions of the parathyroid glands, after surgical removal of an adenoma or of normal parathyroids in connection with thyroidectomy, or during lactation (unusually large amounts of calcium are eliminated with the milk).

Tetanic spasms of the striated muscles, particularly of the extremities, and of some smooth muscular structures, trophic changes of teeth and fingernails, and perinuclear cataracts, are the most conspicuous clinical phenomena of hypoparathyroidism.

In keeping with the low calcium concentration of the blood, *the electrocardiographic Q-T interval is usually prolonged.* Occasional episodes of precordial pain and instances of

Saphir and Corrigan state that "fatty heart" used to be diagnosed frequently by pathologists and clinicians but that the diagnosis has been rare in recent years They quoted Corvisart (1818) as admitting the existence of the entity, but he had not observed it personally and had cited three cases in the literature. White stated that the truth probably lies between the two extreme views that "fatty heart" is common and dangerous or that it does not exist at all as a clinical entity.

PROGNOSIS

Saphir and Corrigan, correlating the clinical findings in 58 autopsied cases, divided the patients into three groups: (1) those in whom *fatty infiltration* was the only cause of death, (2) those in whom it was a contributing factor, and (3) those in whom it was an incidental finding There were two patients in group 1, one of whom died suddenly, 29 patients in group 2 who died of pulmonary emboli, pneumonia, or other disease which could have been tolerated had the heart been normal; and 25 patients in group 3 They mention that fatty infiltration may cause sudden death without premonitory symptoms.

Although the prognosis in obesity is not poor, it is well known that obesity increases operative risk, that mortality rates increase in obesity, and that death rates following trauma are higher in obese patients The part played by the fatty heart is not known.

THERAPY

A sensible program of weight reduction is of prime importance prophylactically and therapeutically. Usual therapeutic measures for myocardial failure should be carried out as necessary.

Obese patients should avoid undue physical strain.

CAUSATIVE FACTORS

Saphir and Corrigan state that general obesity is associated with increased subepicardial fat and the extension of it, and that alcoholic drinks such as malt liquors and sweet wines favor its occurrence. In 136 autopsies on obese subjects, fatty infiltration was found in all (Smith and Willius). White (1951) states that there is a greater tendency to fatty infiltration in obese individuals but that the association of cor adiposum with general obesity is doubtful because of many exceptions: fatty heart occurs in the absence of obesity and obesity is found without fatty heart. Obesity itself puts an added strain on the heart by (1) increasing the body weight, (2) increasing body surface, which requires a tremendous extension of the vascular tree, and (3) increasing the total body metabolism (Willius).

PATHOGENESIS AND PATHOLOGIC CHANGES

In fatty infiltration, fat is grossly deposited in abundance in the subepicardium, infiltrates the myocardium, and replaces some of the myocardial fibers. During routine autopsies, Saphir and Corrigan found a large number of hearts infiltrated with fat, 58 of these were examined closely. The hearts weighed 200 to 800 Gm, mostly 300 to 400 Gm The site of the most extensive involvement was the right ventricle. Fat seemed to follow the course of the coronary arteries along the perivascular spaces and to infiltrate the myocardium The severity varied from moderate infiltration, involving only the outer myocardial layers, to replacement of the entire right ventricular wall In a few instances, subendocardial layers of the left ventricle were involved Microscopically, myocardial changes varied from atrophy to complete replacement of muscle fibers In severe lesions, there were islands of fat discontinuous from the subepicardial fat Preservation of blood vessels was noticeable, and inflammation was absent

Smith and Willius emphasized the fact that excessive amounts of fat were not deposited within the cells as is the case in fatty degeneration.

CLINICAL DESCRIPTION

Heart disease may or may not be present in obesity, and usually there is little or no clinical evidence of it. There may be slight to moderate *dyspnea*, a little *cardiac enlargement*, a little feebleness of the heart sounds, slight reduction in strength of the apical impulse and (rarely) evidence of congestive failure In a clinicopathological conference, P D. White (1954) discussed an obese patient who died after an episode of precordial pain and collapse; no cause of death could be found at necropsy except extensive fatty infiltration of the heart.

Of 136 cases reported by Smith and Willius, heart disease was not evident clinically in 38 per cent, and varying degrees of heart failure were present in 7 per cent which showed no pathological change other than fatty deposition and fatty infiltration of the heart. The remainder had symptoms of heart disease from other causes

Obese individuals often have some exertional dyspnea or the effort syndrome because of the lack of exercise and their excess weight.

TECHNICAL STUDIES

Roentgenographic examination may show some cardiac enlargement, but there are two sources of error in estimating heart size. In stout, obese persons, the diaphragm tends to be high and the heart horizontal; under such conditions the heart appears larger than normal in transverse diameter and area. When the transverse cardiac diameter of a transverse heart approaches the long diameter in measurement, 1 or 2 cm should be subtracted from the transverse diameter, and about 25 cm from the area, in calculating the heart size (White) The other source of error is the presence of a triangular fat pad at the left and, occasionally, the right pericardiodiaphragmatic angles

The *electrocardiogram* in the fatal case discussed by White showed inverted T waves in leads V_1 through V_5 and in lead III, low T waves in leads I, II, aVF and V_6; and R and R′ waves in leads V_1 and V_2

DIAGNOSIS

There is a question about the clinical diagnosis in any case, and fatty heart should only be diagnosed pathologically in the absence of other causes of death. Fatty heart can only be suspected clinically in obese individuals with enlarged hearts or in instances of congestive failure without apparent cause.

case reports, a study by Goodhart and Jolliffe of 83 alcoholics deserves mention· 80 per cent of these showed signs of dietary deficiency, and about one-third had electrocardiographic abnormalities. Dramatic improvement following thiamine therapy is recorded in several reports (Jones et al). Weiss and Wilkins (1937a) observed cardiac changes similar to those of beriberi in a survey of 120 patients with nutritional deficiency. Weiss (1940) concluded that beriberi with cardiovascular manifestations existed in America and Europe. He attributed these manifestations primarily to thiamine deficiency Blankenhorn presented 37 cases of *beriberi heart disease* and described the diagnostic criteria and necropsy findings

Heart disease in the post-partum period closely resembles the disease in alcoholics

the cardiac pathology found in women dying in the puerperium Blacker (1907) and Campbell (1923) pointed out the occurrence of nonvalvular heart disease in the puerperium. Hermann and King (1930) described four cases of myocardial failure of uncertain origin in the puerperium. Williams (1933) stated that 1.5 per cent of cardiac deaths during and soon after pregnancy were the result of "idiopathic" disease Gouley et al. (1937) made a clinical study of seven patients with cardiac decompensation in the puerperium and included autopsy findings in some of them The degenerative changes in the myocardium were emphasized in most reports The clinical findings in 27 patients with post-partum heart disease were described by Hull and Hafkesbring (1937). Sodeman (1940) described two types of failing hearts in the post-partum period; the nephritic and the nonnephritic type. Because

factor Grossly deficient diets were described in a number of the other reports, and attention was drawn to the similarity between the clinical features of cardiac beriberi and post-partum heart disease. The usual manifestations consisted of dyspnea, cardiac dilatation, an accentuated 2d pulmonary sound, gallop rhythm, peripheral edema, and electrocardiographic changes Vilter and McKee (1943) and Mackinon and Mackeen (1949) described further cases of post-partum heart disease. Necropsy revealed degenerative changes in the myocardium. Woolford (1952) described similar cases. Meadows (1957) documented cases from general hospitals

CARDIAC MORPHOLOGY

The following description of the cardiac morphology in post-partum heart disease and heart disease in alcoholics is based on observations in patients at the Cook County Hospital *Both ventricles are hypertrophied and dilated and usually contain adherent and partially organized thrombi* (Figs. 16-10 and 16-11A) *which may give rise to embolic phenomena* Dilatation of the outflow tract of the right ventricle or predominance of right heart involvement, as seen in oriental beriberi, is not a feature. Endocardial fibrosis, if present, is not conspicuous and is then restricted to areas underlying mural thrombi. Microscopically, cellular foci of inflammation are lacking The myocardial fibers exhibit varying degrees of



Fig. 16-10. A Marked dilatation and hypertrophy of the right ventricle with hypertrophy and flattening of the papillary muscle; valves are not involved. Arrow shows mural thrombi B Hypertrophied and dilated left ventricle with mural thrombi between the trabeculae carneae.

11

Nutritional and anemic heart disease[1]

Pathological Aspects

HANS POPPER AND GEOFFREY KENT

Further Pathological Aspects

C. GEORGE TEDESCHI

Clinical Aspects of Vitamin Deficiencies

KARL BRAUN

Clinical Aspects of Anemia, Malnutrition, and Beriberi Heart Disease

PAUL SCHLESINGER AND AARON B. BENCHIMOL

Circulation Time in Beriberi and in Anemia

WILLIAM M. HITZIG

PATHOLOGICAL ASPECTS

The cardiac form of *oriental beriberi*, as described by Aalsmeer and Wenckebach, represents a well-defined clinical and pathological entity Its manifestations are generally recognized to be the result of *vitamin B_1 deficiency*. Other forms of nutritional heart disease have been described in Africa, and they have been provoked in experimental animals The disease encountered in the Bantu differs from oriental beriberi in a number of important clinical and pathological aspects, and has been reported to respond to a well-balanced diet while being refractory to thiamine therapy In the conditions mentioned, impressive clinical and gross pathological features are reflected histopathologically in distinctive, though not specific, regressive changes of the myocardium.

In the large general hospitals of the United States, heart disease is observed which is characterized by *intractable cardiac failure* clinically, and dilatation of the heart chambers with *mural thrombus* formation pathologically. The causative factors usually responsible for such conditions are lacking. Since the disease occurs in *alcoholics* and in women *following the puerperium*, it has been associated with these circumstances, though as yet with insufficient evidence. Similar lesions have been observed in other parts of the western world, e g, Great Britain, France, and Germany They are presented here as a unit with the full realization that they are characterized by the absence rather than the presence of a distinctive set of causative factors.

HISTORICAL BACKGROUND

Cardiac disease in alcoholics or in persons with malnutrition has been recognized for many years Graham Steell (1906) alluded to the cardiac failure of beer drinkers Magniel described cases of heart disease found in association with excessive alcohol intake, manifested by enlarged hearts, gallop rhythm, obesity, and polyneuritis. Of numerous further

[1] Because there are several still incompletely known aspects of these clinical syndromes, four separate contributors will discuss them with some degree of overlapping. *Editor.*

of the heart has been regarded as consistent with beriberi heart disease. The difficulty in reproducing the pathologic lesions of human beriberi in experimental animals (Weiss et al., 1938, Ashburn et al; Wintrobe) does not help to clarify the variations of beriberi heart disease. Failure of beriberi patients to respond to thiamine therapy may conceivably be due to irreversible cardiac changes, perhaps through progression to fibrosis, but this is hard to prove in the individual case, and a cautious attitude toward the diagnosis of beriberi heart disease would seem in order. The designation of *nutritional heart disease* seems preferable in most cases, since a nutritional factor other than vitamin B_1 may be involved. Support for this view is derived from the similarity of many cases to those in the South African Bantu. It must be realized that causes other than malnutrition may produce similar morphologic changes, and in alcoholics, particularly, the toxic effects of alcohol or other toxins must be considered. Since the changes described can be caused by malnutrition, consideration of this origin seems justified in patients who present an obscure picture of cardiac pathology and have a poor nutritional background.

FURTHER PATHOLOGICAL ASPECTS

The response of the heart to injury, regardless of cause, is identical in many instances, owing to the limited capacity of the cardiac structures to react to noxious agents. Degeneration, necrosis of myofibrils, exudative or productive inflammation, and proliferation of fibroblastic tissue are the most common nonspecific responses to injury. It is therefore apparent that, in the absence of an associated lesion regarded as pathognomonic, any attempt to investigate in individual cases the nature of the structural disorder will unavoidably lead into the field of speculation.

The limit of our ability to present etiological diagnosis by a merely morphologic method is clearly reflected by the increasing number of reports which, for obscurity of cause, are placed in the category of the so-called "idiopathic carditis." Myocardial disease which cannot be ascribed to any of the ascertained causes forms an important cardiological problem. Obscurity of cause is not a justification for grouping together obviously heterogeneous conditions, and any effort to link the history of a failing heart to the anatomical observation through the possible causative agent is a step in the proper direction. It is known that the heart is vulnerable to deprivation and that nutrients are particularly necessary to the functional and anatomical integrity of the cardiac structures.

The weight of the heart is decreased in starvation. A diminution in weight of 20 to 30 per cent of normal was found in [illegible]

These data parallel closely those obtained in rats subjected to complete starvation while water was still administered.

The diminution in weight of the organ is mostly due to thinning of the myocardium, which often shows a brownish discoloration, the so-called *brown atrophy*. The subepicardial fat is also reduced in amount and the reduction is usually accompanied by an infiltration of fluid, this results in a gelatinous appearance of the fatty deposits, generally known as *serous atrophy*. The microscopic counterpart is a reduction in the size of the muscle fibers with occasional loss of striations, vacuolization, and fatty degeneration. An accumulation of yellowish-brown granular pigment, largely hemofuscin, is frequently noticeable in the sarcoplasm, usually at the nuclear poles. Hemosiderin granules in proximity to myofibrils have been noted by the author in mice, rats, and rabbits after 5 to 13 days of complete starvation. There was associated atrophy, fragmentation, or hyaline degeneration of myofibrils, and the supporting collagenous framework was condensed in the areas of greater damage. Foci of round-cell infiltration were noticed in some instances between myofibrils, around the walls of blood channels, and beneath the mural endocardium. Since iron is present in cardiac myohemoglobin, it was assumed that the free hemosiderin granules had resulted from lysis of myofibrils.

Follis (1948) has made clear the distinction between "specific" and "nonspecific" alterations resulting from dietary restriction. If all



Fig. 16-11. A. Myocardium with relatively recent thrombus Hematoxylin-eosin. ×85. B. Myocardial fibers showing inter- and intracellular edema. Hematoxylin-eosin. ×260.

degenerative change and, usually, marked *intra- and extracellular edema* (Fig. 16-11B). Lipofuscin pigment around the nuclear poles is commonly seen Occasional foci of fine fibrosis may be present, but the coronary arteries are normal. In general, the patients are in *low-output failure* and present a low pulse pressure, electrocardiographic changes, and gallop rhythm, they do not respond to the usual cardiac regime. The historical and morphologic evidence of malnutrition often includes a poor diet, alcoholism, serum protein changes, the presence of myocardial lipofuscin, loss of basophilia of the pancreatic acinar cells, and failure of the liver to neutralize estrogens, as evidenced by gynecomastia, testicular atrophy, prostatic squamous metaplasia, and pituitary basophilism.

RELATION TO OTHER TYPES OF HEART DISEASE

What is the relationship of these cases to other groups of nutritional cardiopathies? From Africa have come descriptions of two major groups of heart disease. The first, called *endomyocardial fibrosis*, occurs mainly in Southern Uganda and in the Sudan (Davies) (See Chap. 12.) The outstanding pathological feature of this disease is endocardial fibrosis It involves the apical portions of the ventricles and extends into the atrioventricular valves, often rendering them incompetent. The ventricular surface of thickened endocardium is often continuous with blood clot while the deeper layers blend in with fibrotic myocardium. The initial damage is thought to develop in the subendocardial myocardium with subsequent mural thrombus formation and organization. The characteristic localization of the lesion with involvement of the mitral and tricuspid valves, the scarcity of embolic phenomena, and the obscure origin make this condition a distinct one. A similar picture, called *diffuse endomyocardial sclerosis*, has been reported from Europe (Mumme; Lynch), and the United States (Smith et al; McNichol et al.); and there has been some evidence for a nutritional origin The second group from Africa was reported in the Bantu (Becker, Higginson et al.). In these patients, the hearts are enlarged, the ventricles contain mural thrombi near the apex, and the valves are not involved. Endomyocardial fibrosis is not prominent, and embolic phenomena are common Since the Bantu patients with heart disease had liver lesions (presumably due to malnutrition), responded to a dietary regime, and relapsed when put back on their accustomed diet, a good case can be made out for a nutritional origin of this condition The cardiac morphology of alcoholic or post-partum heart disease resembles that described in the Bantu in many ways, but differs from endomyocardial fibrosis.

The distinctive features of *oriental beriberi* are (1) the predominant involvement of the right heart, associated with a prominent pulmonary conus, and (2) its response to thiamine therapy In the later presentations of *occidental beriberi heart disease*, some authors describe a well-defined clinical picture with a good response to thiamine, while others use wider diagnostic criteria and report no therapeutic effect of thiamine. The morbid anatomical features seem no more definite, and involvement of either the right side or both sides

cardium became involved and the degenerative changes were seen to be followed first by leucocytic infiltration and then by fibroblastic proliferation Scarring became apparent around the 87th day, and in rats carried on a low-potassium regime for as long as 327 days, healed lesions were seen side by side with fresh alterations Comparable myocardial changes have been described in dogs, mice, and cattle It has been shown that the reticulin network supporting the myofibrils escapes injury. This may find explanation in the very low potassium content of the connective tissue, almost identical with that of extracellular fluid. The survival of the endothelium lining the mural and valvular endocardium and of the basement menbranes of the blood capillaries, even in the midst of necrotic foci, may also be explained on the basis of the low potassium requirement of these particular structures.

In potassium deficiency, strain is an aggravating factor, on the other hand, rubidium and, to a lesser degree, cesium seem to have a protective effect against the changes of hypokalemia. A protective effect of boron (as boric acid or borax) has not been confirmed Likewise poorly understood is the mechanism of the protective effect of a thiamine deficiency in the hypokalemic rat.

Myocardial lesions similar to those induced by a potassium-deficient diet have been described in rats treated with desoxycorticosterone. Furthermore, when potassium-deficient animals are treated with a cortical hormone, myocardial changes occur sooner and are more extensive than when either one or the other treatment is employed alone. Selye and Pentz suggested that the desoxycorticosterone-produced myocardial lesions resemble those of rheumatic fever, but this identity has not been accepted

Experimental diets deficient in sodium, chlorine, phosphorus, manganese, zinc, and calcium have failed to produce morphological changes in the heart muscle of rats.

Blaxter et al noticed focal myocardial necrosis, hemorrhage, and thrombosis in magnesium-deficient calves. So far, these are the only observations that offer a *morphologic basis* for the disturbances in cardiac function that occur in magnesium deficiency

Bennetts et al found atrophy of myofibrils and replacement fibrosis in cattle grazing in copper-deficient pastures, while Schultze noticed a decrease in the cytochrome activity of heart muscle in rats placed on a low copper regime

Iron is present in cardiac myohemoglobin. Although it is well known that cardiac changes occur in association with anemia, so far myocardial changes have not been found in iron-deficient animals (Follis, 1956).

VITAMINS

The term *vitamin* is usually applied to a number of organic substances, soluble in fat or water, which are needed in minute quantities to maintain the metabolic integrity of the cells. By *vitamer* is meant a structurally related substance having similar biological activity

There is no indication that a *vitamin A deficiency* has any effect on the heart of growing or adult animals. However, Wilson and Warkany observing rats born of mothers fed vitamin A–deficient rations prior to and during gestation, noted an appreciable number of cardiovascular anomalies including structural disorders of the myocardium. Another example of the profound effect which deficiency of a single nutrient at a critical period of growth may have on the development of an organ system is the frequent development of interventricular septal defects, and of abnormalities in the aortic arch derivatives, in the young of rats kept, during gestation, on a diet deficient in pteroylglutamic acid Similar cardiovascular anomalies have been observed in the offspring of rats fed galactoflavin (a riboflavin antimetabolite) during gestation (Baird et al).

It is well established that the cardiac musculature shares with the skeletal muscle the greatest impact of alpha-tocopherol deficiency. Myocardial changes have been demonstrated in rats, rabbits, and calves. Necrosis, loss of striations of myofibrils, nuclear pyknosis, and karyorrhexis, followed by inflammatory reaction and then by fibroblastic proliferation and scarring, is the sequence of changes most frequently encountered. Calcification of fibers has been described in some instances The accumulation in myofibrils of ceroid before necrosis takes place, and the presence of *acid-fast*

Comparable disseminated *myocardial lesions*

the essential nutrients (amino acids, vitamins, and fatty acids) are withdrawn from the diet or are utilized in insufficient quantities, the ensuing changes reflect the general disorder of inanition (*athrepsia*) and are "nonspecific" with respect to a particular deficiency. In the absence from the diet of one or more essential nutrients or in faulty utilization of this or that particular nutrient, "specific" tissue alterations take place. However, this does not mean pathognomonic in a morphologic sense.

The advent of purified rations and crystalline vitamins has opened a new alley in the investigation of the effects of selected dietary deficiencies. Spontaneous diseases secondary to certain dietary deficiencies occur in man, but preceding, associated, interdependent, or intercurrent disorders from other causes often make difficult the evaluation of the physiological and morphological changes which are directly due to the dietary deficiency. It is therefore not surprising that most of our knowledge of "specific" nutritional disturbances is based on the results of observations in the experimental animal, in which controlled conditions are more easily achieved.

When the concentration of a particular nutrient in the tissues of the heart falls to a critical level, a metabolic derangement takes place which reveals itself by various degrees and types of disturbance. This disturbance can manifest itself by alterations in function, appearance of abnormal metabolites in blood or excreta, or morphological deviations from the normal. The latter may be so pronounced as to be detected by the naked eye, or may be of microscopic or submicroscopic dimensions. Recent advances in the field of histochemistry have made it possible to demonstrate directly particular nutrients, such as riboflavin or vitamin A, within the cells in tissue sections.

The above course of events does not take place in every instance and a sequence is not always demonstrable. The deficient state can be so severe and abrupt as to induce an overwhelming functional disorder which is incompatible with life, and in this case morphological changes may be slight or even absent, or the deficiency may be of longer duration, but less severe in degree, and in this case structural alterations take place This is well exemplified by Follis' observations (1943) on the response of the swine heart to acute or chronic thiamine deficiency. In the acute experiment the animal dies, ostensibly of heart failure, with virtually no myocardial structural change; on the other hand, in the animal which withstands a lesser degree of dietary deficiency for a longer time, myocardial alterations become visible.

Of the 96 elements which are now known, seventeen or eighteen are indispensable to the maintenance of normal cardiac metabolism and structure.

AMINO ACIDS

Amino acids are generally classified as *non-essential:* those which can be synthesized by the organism; and *essential:* those which must be furnished preformed in the diet Available information indicates that upon withdrawal from the diet of all of the essential amino acids, no striking myocardial alterations, either in function or in structure, take place.

INORGANIC ELEMENTS

Since the classic observations of Ringer, the importance of potassium in the normal functioning of the heart has been well recognized. The term "hypokalemic myocarditis" has been proposed to indicate the lesion occurring in patients with potassium deficiency, and the condition is now listed in the Cardiovascular Registry of the Armed Forces Institute of Pathology. The lesion consists mainly of focal myocardial necrosis followed first by macrophagic and lymphocytic reaction, and in later stages by fibroblastic proliferation and scarring. Myocardial alterations interpreted as hypokalemic have been described in Cushing's syndrome, in desoxycorticosterone treatment, and in certain types of chronic nephritis; in one instance fresh necrosis has been shown in Addison's disease. It is not clear whether potassium deficiency alone or its combination with some other metabolic disturbance is responsible for these changes.

Experimentally, Follis et al. (1942) have traced the sequence of changes that occur in the rat's heart after the rat is placed on a diet deficient in potassium. Below a critical potassium level, alterations were noticed as early as the eighth day. These changes were focal in distribution and consisted mainly of loss of striations, lysis, and necrosis of myofibrils As the deficiency progressed, larger portions of myo-

cardium became involved and the degenerative changes were seen to be followed first by leucocytic infiltration and then by fibroblastic proliferation. Scarring became apparent around the 87th day, and in rats carried on a low-potassium regime for as long as 327 days, healed lesions were seen side by side with fresh alterations Comparable myocardial changes have been described in dogs, mice, and cattle. It has been shown that the reticulin network supporting the myofibrils escapes injury. This may find explanation in the very low potassium content of the connective tissue, almost identical with that of extracellular fluid. The survival of the endothelium lining the mural and valvular endocardium and of the basement menbranes of the blood capillaries, even in the midst of necrotic foci, may also be explained on the basis of the low potassium requirement of these particular structures.

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Comparable disseminated myocardial lesions

have been described in ducklings placed on biotin-deficient diets and in guinea pigs kept on a diet deficient in ascorbic acid. Rinehard and Mettier used guinea pigs to study the combined effect of scurvy and beta-streptococcus infection and noticed, both in the myocardium and in the valvular endocardium, lesions which resembled Aschoff bodies. They suggested that rheumatic fever might be a response of scorbutic tissue to streptococcal infection, but similar changes were obtained by others in ascorbic acid deficiency alone.

Myocardial changes have not been found in animals deficient in *niacin* or in *vitamin* B_{12} (Follis 1956). Tissue slices of ducklings kept on *pantothenic acid*–deficient diets have shown lowered oxygen consumption and pyruvate utilization. Coenzyme A reduction was also lowered as much as 80 per cent, both in the atria and ventricles, in the absence of structural alterations. A reduction in transaminase activity in heart tissue homogenates has also been shown in pyridoxine-deficient rats but, as in the case of the pantothenic acid–deficient animal, the metabolic disorder is not accompanied by demonstrable anatomic lesions.

Among the nutritional deficiency states affecting the heart, major interest has revolved about the effect of *thiamine* deficiency. Deficiency of the thermolabile portion of the vitamin B complex has long been recognized as the chief cause of beriberi. Cardiac failure is one manifestation of this deficiency; the so-called "beriberi heart." Clinical and experimental evidence leaves little doubt that the functional disorder results from a structural defect. However, the character of the anatomical change in the human heart is still a matter of dispute. There is controversy whether the chambers of the right side are both hypertrophied and dilated or merely dilated. According to Vedder the heart is always considerably enlarged, particularly on the right side. The average weight reported by Dock was 629 Gm. On the other hand, in the series of Weiss and Wilkins (1937) the weight of the heart was normal in 21 of 30 autopsied patients. Keefer and Wenckebach (1938) both state that the right ventricle is often dilated, most prominently in the region of the pulmonary conus.

Histologically, loss of striations, fragmentation, hydropic or fatty degeneration, necrosis, sarcolysis of myocardial fibers, separation of muscle bundles by edema fluid, swelling of collagen, perivascular edema, and occasionally small lymphocytic and leucocytic infiltrations have been noticed by several investigators. Smith and Furth and Toreson have postulated that certain cases of endocardial and subendocardial fibrosis in young adults which cannot be explained on the basis of arteriosclerosis, hypertension, or rheumatic heart disease, might represent a variant of "beriberi heart" caused by prolonged dietary deficiency.

Among the various changes, particular attention has been called to the hydropic degeneration of the myofibrils and to the interstitial edema. It has been suggested that these alterations are due to water retention in the cardiac muscle. However, Jolliffe and Goodhart found no difference in the water content of human hearts in nutritional-deficient states with or without heart failure, or in organic heart disease with anorexia, as compared with the water content of the hearts in a normal control group.

Since *alcohol addicts* consume an inadequate amount of many of the essential elements of nutrition, it is not surprising that they may undergo cardiovascular disturbances similar in many respects to those described in patients with beriberi heart. The morphologic counterpart was found also to be similar and Oppenheim does not hesitate to interpret the myocardial alterations of patients with liver cirrhosis as manifestations of a hepatogenic metabolic disorder. As in beriberi heart, these myocardial alterations are not pathognomonic and it must not be assumed that they are produced merely by thiamine deficiency. However, the contention that thiamine deficiency in the human being leads to myocardial damage is well supported by observations on experimental animals. Microscopic lesions have been demonstrated in animals of various species placed on thiamine-deficient diets. These experimental lesions also, although characteristic, are not specific or pathognomonic, consisting mainly of vacuolization and necrosis of myofibrils in the early phases, and of fibrosis and scarring in animals with a longer survival period.

Large amounts of sodium pyruvate accumulate in the absence of thiamine, it has been indicated, however, that it is not the excess of

pyruvate which causes the cardiac disturbance in thiamine deficiency.

The close similarity of the cardiac lesions resulting from deficiency of potassium or thiamine has been emphasized by several investigators Well-established also is the intimate relationship of both potassium and thiamine to carbohydrate metabolism. More severe alterations should therefore be expected to occur when both essential nutrients are deficient in the diet. On the contrary, well-conducted experiments have shown a mutually protective effect of combined potassium and thiamine deficiencies

In addition to the fact that thiamine deficiency may be a primary cause of cardiac disorder, it must be pointed out that organic heart disease per se may constitute a conditioning factor in the development of thiamine deficiency. Anorexia is frequently associated with congestive failure. Congestive changes in the liver, stomach, and intestines are frequently superimposed features. All these disturbances unavoidably lead to restriction of food intake and impaired absorption and utilization. Further depletion of thiamine stores can also be expected to occur following mercurial diuresis, and if the deficiency reaches a level which is incompatible with the structural integrity of the cardiac muscle, it is obvious that the added damage will aggravate the underlying cardiac condition

CLINICAL ASPECTS OF VITAMIN DEFICIENCIES

GENERAL CONSIDERATIONS

Vitamin deficiencies may be classified as *primary* and *secondary* deficiency states. The single responsible factor in the "primary" state of deficiency diseases appears to be a chronically deficient diet. Secondary deficiency disease is caused or *precipitated by a recognizable disease without a grossly deficient* diet. The main factors in the development of secondary deficiency are (1) loss of vitamins (diarrhea, polyuria), (2) increased requirement due to elevated metabolism (fever, thyrotoxicosis, infections, pregnancy, growth, and excessive physical activity); (3) faulty absorption, utilization, and assimilation (gastrointestinal diseases, diseases of the pancreas, and disorders of the liver), (4) inability to store vitamins (diseases of the liver) These conditions may be present as single factors or in a combined form. "Secondary" deficiency diseases are more common, in a series of 50 consecutive patients, who had vitamin deficiencies and who were treated by the author, 46 were found to belong to this group (Braun and Kornbluth)

Vitamin deficiencies are known *to cause functional* or structural changes in the gastrointestinal tract and the liver, thus interfering with the normal utilization of vitamins and aggravating the deficiency syndrome Though some of the conditioning factors may be *apparent*, it has been demonstrated that, in a group of persons consuming identical diets, some develop vitamin deficiency while others do not It is probable, therefore, that intrinsic factors are also involved in the *pathogenesis* of deficiency diseases The vitamin requirements may vary considerably with the type of diet ingested *Thiamine* requirements are higher on the high-carbohydrate, low-fat diet of the Orient than on the usual Western diet (see Part 2, Chap. 31) A carbohydrate- or maize-rich diet may provoke the appearance of vitamin B deficiencies (thiamine, niacin) because of the increased need for *cocarboxylase* (*thiamine* pyrophosphate) and *coenzymes I and II*, which are essential for the breakdown of carbohydrates. *Patients with* disturbed carbohydrate metabolism, as in *diabetes mellitus*, may require larger amounts of the B *vitamins*, especially when the carbohydrate intake is increased, as in the treatment of diabetic acidosis

Replacement of food by *alcohol* may lead to the development of deficiency manifestations because of decreased intake of proteins, thiamine, *niacin*, and *riboflavin* Finally, climate could be considered a *factor in this* development Hyperthermia *increases the* rate of catabolic processes in the body, and it has been shown that the amount of thiamine necessary *for* utilization of 1 Gm of food at a temperature of 91°F *is* twice as large as that required at a temperature of 61°F.

According to Darby, the spectrum of *nutriture* (condition as to nourishment) *ranges* from the zone of excess to that of clinically manifest *severe deficiency* disease The following zones have been defined. (1) excess zone; (2) saturated zone, (3) unsaturated *and functionally* unimpaired zone, (4) potential *deficiency* disease; (5) latent deficiency disease, and (6) *clinically* manifest deficiency disease. The last three zones are of importance to this study and will be *dealt* with more fully. "Potential deficiency disease" *is a syndrome* which

exists without any clinical signs of vitamin deficiency but in which a new stress will cause a rapid development of the clinical manifestations. Biochemical tests, tolerance or saturation, will show evidence of a decreased reserve of vitamin stores.

"Latent deficiency disease" is the mildest clinically detectable deficiency state. It is characterized by nonspecific symptoms, such as irritability, gastrointestinal disturbances, and insomnia. The diagnosis is established by the aid of biochemical tests and by therapeutic trial.

The "clinically manifest deficiency diseases" include those mild and severe states which show specific functional and structural alterations.

Deficiency diseases are rarely the result of one single vitamin deficiency. *Beriberi* patients may show signs of niacin deficiency, and *pellagra* patients often show signs of riboflavin deficiency. Insufficient intake of vitamins is often accompanied by nutritional macrocytic anemia or edema due to hypoproteinemia One example of this type of disorder is *kuashiorkor*, a disease characterized by *hypoproteinemic edema* and *pellagrous dermatitis* (C. D. Williams, 1953). It should be emphasized, however, that total caloric depletion is rarely accompanied by deficiency syndromes.

THIAMINE DEFICIENCY (BERIBERI)

Definition. The clinical syndrome of thiamine deficiency is characterized by the following manifestations. cardiovascular involvement, multiple neuropathy, and edema. These manifestations are curable by thiamine administration.

Pathogenesis. *Thiamine* is a water-soluble, heat-labile vitamin, the daily human need of which is about 2 mg. Thiamine serves as a part of the enzyme cocarboxylase, which is thiamine pyrophosphate, and functions in the breakdown of glucose. The principal sources of this vitamin are lean meat, whole cereals, nuts, yeast, and legumes Polished rice and refined cereals are practically devoid of the vitamin

In the *Oriental population,* beriberi is usually due to inadequate diet and seems to be one of the pure forms of thiamine deficiency Major outbreaks of beriberi have been observed in China, Japan, Brazil, South Africa, the Philippines, and Malaya The importance of polished rice as a contributory factor and the rice pericarp as a preventive, was recognized early in the history of this disease. In the United States, the "maladies des jambes" resembles the Oriental beriberi, and is also the result of a diet consisting mainly of polished rice (Scott and Herman).

Occidental beriberi is most frequently a result of chronic alcoholism. It has been demonstrated that alcohol per se does not play a direct role in this disease, since the clinical picture could be completely reversed by administration of thiamine to patients who maintain their usual intake of alcohol. Furthermore, the disease has been observed in alcoholics even after a period of several months of total abstinence from alcohol. Because of its high caloric value and the harmful effects it has on the gastrointestinal tract, alcohol is an important predisposing cause of thiamine deficiency. Fatty degeneration or atrophic cirrhosis of the liver may interfere with the proper assimilation and storage of this vitamin Alcoholic beriberi develops more frequently in persons consuming "hard liquor," such as gin or whisky, but is also found among heavy beer drinkers. In a series of 22 patients with alcoholic beriberi, excessive physical activity was felt to be a contributory factor, inasmuch as all but six were engaged in heavy physical work (Benchimol and Schlesinger).

Clinical Features. Cardiac and nervous manifestations in the Western Hemisphere are essentially the same as those occurring in the Orient, being influenced by the degree and duration of the deficiency state and the rapidity with which the avitaminosis develops. The clinical picture may appear as one of three types· (1) *cardiovascular beriberi,* which appears in an acute, subacute, and chronic form, (2) *wet beriberi,* in which anasarca is a prominent feature; and (3) *dry beriberi,* in which the involvement of the nervous system is predominant. These three forms may appear separately or may be combined *Shoshin* is an acute form characterized by severe dyspnea, tachycardia, restlessness, water retention, and precordial pain. Unless treated immediately, patients with this syndrome die within 3 days from circulatory collapse Aalsmeer and Wenckebach and Weiss and Wilkins have described the symptoms and signs of the subacute and chronic forms of beriberi. Whereas the former have noted only right-sided failure in the Orient, the latter have observed patients with both left- and right-sided failure in the Occident. The patient is nervous and restless, and complains of fatigue and pain over the

calf muscles, which are enlarged and hard. *Precordial pain, palpitation,* and *shortness of breath* may be present. Upon examination, the skin is warm and there is often high temperature. Varying degrees of *dyspnea* and *edema* are noted The heart is usually enlarged on percussion to both right and left. There are visible and palpable pulsations over the precordium, at the left of the sternum. *A triple rhythm*, a weak 1st sound, and *systolic as well as diastolic murmurs*, may be heard The pulse is frequently rapid, but bradycardia was also noted. The blood pressure may be elevated, normal, or low. An increased pulse pressure with a *water-hammer* type of pulse may be present, and *pistol-shot sounds* may be heard over the femoral artery. Signs of right heart failure, e.g, neck vein congestion, enlarged painful liver, and serous effusion, are frequently found The phenomena of peripheral arterial vasodilatation, however, may be absent, and the clinical picture may simulate other types of heart disease

The venous pressure is markedly elevated, circulation time is generally normal or only slightly prolonged However, Benchimol and Schlesinger noted a prolonged circulation time in about half of their patients *Bradycardia*, associated with other signs of vagal activity, such as hyperactive carotid sinus, was observed during convalescence

Roentgenological examination may reveal either cardiac enlargement (Fig 16-12) or a normal silhouette. Aalsmeer and Wenckebach emphasized the dilatation of the right heart with a prominent pulmonary artery, similar to the profile of the heart in mitral stenosis In the Occident, however, cardiac enlargement of both the left and right heart chambers is more frequent, and pulmonary congestion is present in most cases The cardiac dilatation is not always completely reversible following treatment, apparently due to structural and irreversible myocardial involvement which prevents complete normalization



Fig 16-12. A Case of beriberi The cardiac shadow is enlarged to both the left and right. The hilar markings are increased, congestion of the lung at the right base B After treatment with thiamine, the cardiac shadow became normal and the lung markings decreased

Electrocardiographic Changes. In *Oriental beriberi*, the electrocardiogram is often normal or shows only a shortening of the P-R interval In *Occidental beriberi*, the electrocardiogram may show various abnormalities which are nonspecific in about 90 per cent of patients These changes represent an important feature of Occidental beriberi. They consist mainly of abnormal ... *T waves inverted.* ... be prolonged The S-T segment is generally isoelectric. The ventricular complexes are of *low voltage*, and *intraventricular conduction disturbances* may occur (Fig 16-13). These changes disappear with varying rapidity following specific treatment Electrocardiographic signs of left ventricular hypertrophy were present in about 50 per cent of the cases in a series. It may be difficult to distinguish these cases from the average hypertensive patients, particularly because the blood pressure is sometimes elevated in beriberi heart disease. A temporary

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water retention. Metabolic studies suggest that *increased cellular osmolarity* caused by the accumulation of pyruvate and lactate ions in the tissues may be the primary factor provoking retention of sodium and water.

Excessive posterior pituitary secretion and increased aldosterone production may contribute to the salt retention, just as in the low output type of heart failure. Guggenheim studied the effect of water load in thiamine-deficient animals, he found that the impaired ability of the liver to inactivate the antidiuretic hormone is an important factor in the development of beriberi edema. Since nutritional cirrhosis occurs frequently in beriberi, these experiments appear to have some clinical confirmation.

Metabolic Changes in the Heart Muscle. Metabolic disturbances occurring in the myocardium have been implicated in the causation of heart failure. Since thiamine diphosphate serves as a cocarboxylase in the oxidation of pyruvic acid, *the characteristic derangement* of the beriberi heart is *inadequate breakdown of pyruvate from the heart.* Raab (1955) believes that thiamine deficiency is characterized both by deficient oxidation of myocardial pyruvate and exaggerated accumulation of catecholamines in the heart muscle (Chap. 10 and Part 2, Chap. 29). He states that the cardiac manifestations can be explained by these changes It is at present the consensus, however, that neither the structural nor the metabolic changes in the myocardium are sufficient per se to explain the sequence of events leading to the heart failure of beriberi. As previously stated, a peripheral vascular mechanism must also be taken into consideration

Pathological Findings. The alterations of the myocardium have been studied extensively, but no pathognomonic picture has been revealed *Dilatation* and *hypertrophy* of both the left and the right heart chambers may be found at autopsy. Generally, the myocardial lesions are not marked and consist of *mild interstitial and intracellular edema*, and *degenerative changes* This would not account for the myocardial failure Autopsy findings, moreover, may be completely normal, particularly in the very acute phases, when the metabolic derangement leads to death prior to the development of anatomically recognizable lesions In animal experiments, on the other hand, deprivation of vitamin B_1 causes *necrosis of muscle fibers* and cellular infiltration and proliferation, as well as moderate fibrosis in the atrial musculature.

Diagnosis Diagnosis is based on the history of poor dietary intake, sometimes with chronic alcoholism, signs of congestive heart failure of the high output type, elevated venous pressure, normal circulation time with increased pulse pressure, and warm skin. Laboratory examinations show electrocardiographic *abnormalities* and roentgenological changes. The absence of pericardial, valvular, or other forms of heart disease is diagnostically important. In the differential diagnosis, the various conditions leading to high output failure, e g , hyperthyroidism, cor pulmonale, arteriovenous fistula, anemia, and Paget's disease, should be considered.

Many laboratory procedures have been used for the diagnosis of thiamine deficiency The *load test* determines the urinary excretion of thiamine in 4 hr following standardized doses of the vitamin. Diminished urinary excretion of the vitamin is characteristic of deficiency Tests based on an impairment of the metabolism of pyruvic acid seem to be more reliable for the diagnosis of thiamine deficiency. Elevated blood pyruvic acid values (over 1.2 mg/100 ml) are frequently found in beriberi To increase the sensitivity of this test, administration of glucose and the performance of exercise have been advocated

Treatment. Curative treatment should be given parenterally in the acute stage. *Ten to fifty* milligrams of thiamine hydrochloride should be administered Once response has begun oral administration, 5 mg three times a day, *should be instituted. Allergic reactions to* parenteral vitamin B_1 administration have been reported. A concentrated protein-rich diet should be given simultaneously, alcoholism should be treated and faulty dietary habits corrected. Other accompanying deficiency diseases have to be treated specifically Some investigators suggest the use of *digitalis* when signs of peripheral *congestion* are present, while others claim that this drug is ineffective

Prognosis. Prognosis depends upon the progress of the disease. In the very acute form (*shoshin*), the prognosis *is bad* unless proper therapy is immediately instituted In the less acute forms, therapy results in a *rapid remission* of symptoms and signs Lack of response

Fig. 16-13. Intraventricular block in a case of vitamin B deficiency. *The first electrocardiogram shows widened ventricular complexes and isoelectric T waves. The second electrocardiogram, after nine days of treatment with thiamine and niacin, is normal.*

deterioration of the electrocardiogram in some cases, in spite of clinical improvement, has been noted. Arrhythmias are rarely seen.

Pathologic Physiology. Weiss and Wilkins and Porter and Downs stressed the peculiar state of the circulation, which is a combination of overactivity and failure of the heart. They described the *rapid velocity of blood flow*, the *dilatation of the arterioles*, and the *small arteriovenous oxygen difference* The similarity of this syndrome to thyrotoxic heart disease and to the failure which occurs in large systemic arteriovenous fistula was stressed The common characteristic feature in these disease states is a reduced peripheral resistance. Hemodynamic studies made possible by cardiac catheterization have confirmed the finding that *the cardiac output in beriberi is elevated* Burwell and Dexter were the first to study a patient with beriberi disease by this method. They found a small arteriovenous oxygen difference, a twofold elevation of right ventricular and pulmonary arterial pressure, and a markedly increased cardiac output. After treatment with vitamin B_1, there was normalization of cardiac output and pressures. Lahey et al. observed normal right heart and pulmonary arterial pressures with markedly increased cardiac output and a small arteriovenous oxygen difference. A remarkable observation in their study was the *very high peripheral venous pressure while right atrial pressure was normal.* This right atrial–peripheral venous pressure gradient is *the reverse* of that usually seen in right heart failure with low cardiac output. The fall of the peripheral venous pressure after thiamine administration with an unchanged *mean* atrial pressure, together with the above finding, suggested that the early peripheral venous hypertension was largely *the result of transmission of the arterial pressure through a dilated arteriolocapillary bed.* In arteriovenous fistula, a similar shunt occurs directly from a large artery to a large vein, but the venous valves block widespread transmission of the arterial pressure. No such protection exists in beriberi in the capillary bed and the effect therefore becomes generalized. Further, the increased capillary pressure favors the development of edema, even before the right heart is embarrassed by the excessive venous return and before the end diastolic ventricular pressure becomes elevated. This conforms with the observation that congestion and edema may be present even with normal-sized hearts Compensatory *hypervolemia* may be present, and this may lead to an increased inflow load and eventually to overstretching of the myocardium and frank failure. It follows, therefore, that *high output circulatory failure* may be observed with normal or with elevated right ventricular pressures (Youmans). These hemodynamic changes explain the increased sensitivity to injected epinephrine which had already been noted by Shimazono. Administration of a vasoconstrictor drug may cause a sudden shift of a large amount of blood from the systemic circuit into the already engorged pulmonary circulation, thus elevating the pulmonary capillary pressure to edema level

The mechanism of the *salt and water retention* in this type of high output circulatory failure has been studied (Isen et al.; Lahey et al). *It was found* that the ratio of the renal blood flow to the systemic flow was greatly *decreased* and an oliguric response to a water-load test was noted These authors assumed that the alteration in the distribution of volume flow as a consequence of shunting blood away from the kidney is responsible for the salt and

sociated with normal electrocardiograms. Since niacin is the chemically active fraction of coenzymes I and II, which are essential for the intermediate metabolism of the carbohydrates, it was assumed that *the electrocardiographic changes are the result of an altered metabolic state* in the heart muscle. This view is supported by the fact that a marked diminution of coenzyme I was found in the *striated muscle* of human subjects deficient in niacin (Axelrod et al.). In another study, electrocardiographic abnormalities occurring during the convalescent period of typhoid fever were investigated (Braun and Grossowitz). It was shown that alterations of the ST-T segment occurred concomitantly with the reduction of the urinary excretion of niacin in 35 out of 50 patients with typhoid fever. These observations and the favorable effect of niacin on the electrocardiogram were considered as evidence that electrocardiographic abnormalities are due to niacin deficiency. Finally, in experiments on the isolated perfused heart, the administration of the niacin antagonist, 3-acetylpyridine, caused marked electrocardiographic abnormalities which could be prevented or abolished by niacin administration (Braun, 1949).

Summarizing, it seems that pellagra is accompanied by specific electrocardiographic changes, but there is no evidence of hemodynamic alterations in the cardiovascular system

DISEASES PROBABLY RELATED TO VITAMIN B OR NUTRITIONAL DEFICIENCY

Increased attention is being given to certain obscure cardiopathies and their relation to nutritional deficiency Bedford and Konstam described a series of 40 African soldiers with cardiomegaly and signs of heart failure. Autopsy in 17 of the cases revealed endocardial fibrosis, some subendocardial necrosis, and a hypoplastic aorta. The coronary arteries were normal The origin of the disease could not be established but they considered nutritional or constitutional factors as causative. Davies and Ball observed a very similar condition in African natives *Endomyocardial fibrosis* was found to be the cause of death in 32 of 231 consecutive autopsies in Uganda (Chap. 12). A disease seen in Bantus and other tribes of South Africa, which has been called *cardiovascular collagenosis*, belongs in the same class. In the Occident, a similar condition has been observed (Byron). Smith and Furth described a patient with cardiac fibrosis involving the subendocardial layers of both ventricles and associated with mural thrombosis. Dock described five cases of marked cardiac hypertrophy with mural thrombosis and embolic accidents involving the systemic and pulmonary circulation. *In all these conditions, nutritional deficiency, particularly of the B vitamins, was suspected as a causative factor.*

Congenital fibroelastosis occurs very early in life and the large majority of patients die in the first year. It is frequently accompanied by other congenital anomalies of a serious nature, mainly aortic lesions. There are apparently two varieties of the disease, fetal and infantile. The latter is less frequently accompanied by congenital lesions and the chances of survival in childhood are better. The nutritional aspects of this disease have not yet been extensively investigated, but nutritional failure of the pregnant woman has been suspected as a cause, even though so far definite proof is missing

CLINICAL ASPECTS OF ANEMIA, MALNUTRITION, AND BERIBERI HEART DISEASE

The importance of certain nutritional disorders as causative factors in heart disease has been pointed out in the medical literature, emphasizing the practical therapeutic implications which result from a more precise diagnosis of these conditions

It is known that a number of deficiency states may be *solely* responsible for cases of advanced congestive heart failure as observed in beriberi heart disease (Benchimol) and in the so-called "nutritional heart disease" recently described in South Africa by Gillanders and by Higginson et al. The latter have attributed this syndrome to a dietary deficiency, since the clinical picture could be partially or completely reversed by an adequate diet.

Of greater importance, although neglected in most textbooks of cardiology, is the contributory role of these factors in the unfavorable course of certain cases of heart failure, pri-

to therapy has been noted in some cases and was attributed to irreversible myocardial damage.

PELLAGRA

Pellagra is a deficiency syndrome characterized by dermatitis, glossitis, dementia, and diarrhea.

Pellagra is the result of *niacin* deficiency. Protein depletion is a contributory factor, since it has been demonstrated that the amino acid tryptophan may serve as a precursor of niacin. Pellagra appears frequently as a secondary deficiency state.

Cardiovascular symptoms have been observed in pellagra, particularly in the acute form. The symptoms are *dyspnea on exertion* and *palpitation*. Cardiac enlargement and venous congestion have not been noted. *Electrocardiographic abnormalities* consisting mainly of alterations of the ST-T segment have been described by Feil in about 40 per cent of patients but were attributed to B_1 deficiency. Mainzer and Krause suspected a causal relationship between the electrocardiographic abnormalities and niacin deficiency. In one of their patients, the administration of niacin was followed by normalization of the electrocardiogram. Various abnormalities of the ST-T segment were demonstrated by Rachmilewitz and Braun (1945a) in 18 of a series of 27 patients with pellagra (Fig. 16-14). Therapeutic tests carried out in various phases of the disease proved that the electrocardiographic abnormalities promptly disappeared following treatment with *niacin* while administration of thiamine had no visible effect. They observed that there was a parallelism between the electrocardiographic abnormalities and the visceral manifestations of the disease. The most striking changes were seen in patients having mental and gastrointestinal disturbances, sometimes in the absence of dermatitis. On the other hand, the presence of skin lesions alone in chronic pellagrins who show no obvious involvement of the visceral organs may be as-

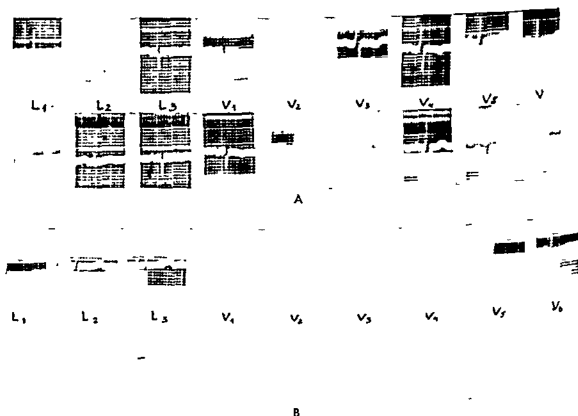


Fig. 16-14. A. Electrocardiogram in a case of pellagra. Note isoelectric and inverted T waves in the upper record. After treatment with niacin, the T waves became normal (lower record). B. Electrocardiographic abnormalities appearing during convalescence from typhoid fever. In the upper record the Q-T interval is prolonged and the T waves are inverted in L_1 and in the chest leads. After 4 days of treatment with niacin, the electrocardiogram shows normal ST-T segments (lower record).

of appropriate medication, a fact which has been attributed to the occurrence of irreversible hypertrophy.

Figure 16-15 illustrates the decrease in heart size observed in a patient with hookworm anemia following the normalization of the blood count and hemoglobin level as a result of the oral administration of ferrous sulfate.

The mechanism of cardiac enlargement in anemia has not yet been established. The present trend is to consider this type of cardiomegaly as a nutritional deficiency of the myocardium due to chronic hypoxia (Lewis et al.), although one cannot discard the effect of the hemodynamic changes which overload the heart. In favor of this are the clinical observations of Hunter; in his cases, dilatation and hypertrophy did not result from myocardial hypoxemia, since the reduction in heart size occurred in the initial stage of treatment, when the hemoglobin level was still well below normal levels These cases do not suggest an immediate improvement of the hypoxemic heart but rather the influence of the hemodynamic changes.

The heart sounds are usually altered in anemia. At the apex, the 1st heart sound is generally increased in intensity, and there is a *loud 3d sound* Murmurs appear frequently, particularly in the severe cases, and may be loud enough to simulate organic valvular disease. *Systolic and diastolic murmurs* may be heard over the entire precordium, particularly in advanced cases of sickle-cell or pernicious anemia. The systolic murmurs are due to rapid circulation, as well as to dilatation of the cardiac chambers and the AV rings. *Diastolic murmurs* are observed in anemic patients in the absence of organic heart disease, simulating either aortic insufficiency or mitral stenosis. They are due to the dilatation of the aortic and pulmonic valvular rings as well as to dilatation of the ventricles (relative mitral and tricuspid stenosis).

In addition to these cardiac murmurs, a *venous hum* may be heard over the neck veins and the supraclavicular area.

Nonspecific electrocardiographic changes may be observed, such as S-T depressions, low voltage or inversion of the T waves, and, rarely, low voltage of the QRS complex. This will increase in amplitude following appropriate therapy (Figs 16-16, 17). There is some controversy regarding the frequency and importance of the electrocardiographic changes in chronic anemia. According to a number of publications they occur in approximately 20 per cent of all cases and are usually not marked (Porter et al; Wilbus et al.) although they

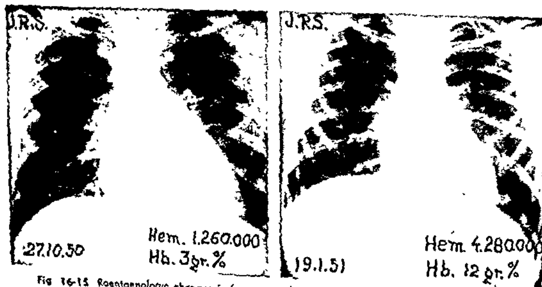


Fig 16-15 Roentgenologic changes in heart size observed in a 15-year-old patient with severe hookworm anemia Cardiac enlargement is evident in the initial x-ray film at which time the erythrocyte count was 1,260,000 and the hemoglobin level 3 Gm per cent. Following appropriate therapy there is a marked reduction in heart size, which occurred 3 months later together with a practically normal blood count

marily due to other causes. Thus, it is not rare to see a patient in failure who is refractory to the usual therapy until additional measures correct an associated deficiency state (anemia, hypoproteinemia, or thiamine deficiency).

On the other hand, these nutritional disorders may be secondary to the heart failure itself, because of several circumstances which predispose to them.

It is known that patients in failure often complain of poor appetite, either as a result of visceral congestion or of the effect of certain drugs, such as digitalis or ammonium chloride. In addition, the following factors must be taken into account: disturbances of gastrointestinal absorption, excessive diuresis due to the frequent administration of mercurial diuretics which eliminate significant amounts of water-soluble vitamins, and the dietary restrictions imposed upon these patients. The widespread indication of sodium restriction in the treatment of the congestive manifestations, although of great value in such cases, undoubtedly contributes to the unpalatability of the diet and leads to anorexia with consequent malnutrition. Finally, it should be emphasized that increased metabolic needs may supervene in decompensated patients in the course of infections, hyperthyroidism, or pregnancy, leading to the relative inadequacy of a diet which would be appropriate under normal circumstances.

The need for a proper recognition of the above-mentioned factors is emphasized by cases in which these associated conditions interfere with the effect of drugs leading to the apparent irreversibility of heart failure A number of these instances of *refractory failure* are actually due to the frequently unrecognized presence of one or more of these factors, which are usually controllable with appropriate therapeutic measures

The cardiovascular effects of the following deficiency states will be described below: (1) anemia, (2) malnutrition and starvation, including the effect of hypoproteinemia; (3) other types of deficiency, (4) beriberi

ANEMIA

Long-standing severe anemia, regardless of its origin, often results in various cardiovascular manifestations, either by causing degenerative changes in the hypoxic cardiac muscle or by overloading the heart as a result of hemodynamic changes.

Anemic states often represent aggravating or precipitating factors of heart failure in patients with other types of heart disease However, they occasionally constitute *the sole cause* of heart failure. *Any type of anemia of severe degree and of long duration may determine circulatory changes.* Thus, in sickle-cell anemia, which as a rule does not respond favorably to therapy, these changes are more marked, and may resemble rheumatic valvular disease. However, even certain reversible forms of anemia (such as pernicious anemia and the type due to hookworm infestation) often lead to cardiac involvement if they are not properly treated. It is in these conditions that the role of anemia in heart disease may be observed, since the effects on the cardiovascular system disappear rapidly following appropriate therapy.

The basic pathophysiology of the cardiovascular system in anemia is due to various adjustments in the diminished *oxygen-carrying capacity* of the blood. In order to maintain an adequate oxygen supply to the tissues, several mechanisms may operate in anemia Thus, the velocity of blood flow is *increased*, probably as a result of peripheral vasodilatation caused by the accumulation of acid catabolites, in addition to a decrease in blood viscosity.

There is also an increased percentage of oxygen utilization by the tissues, and cardiac output is considerably greater due to rapid circulation and greater venous return to the heart. *Anemic heart disease* illustrates a type of heart failure which is associated with an increased cardiac output.

Notwithstanding the greatly augmented cardiac output, the heart may not be overloaded (Stewart et al , 1937), and this is explained by a drop in peripheral resistance and a lower blood pressure resulting from vasodilatation and lowered blood viscosity. However, in cases of severe chronic anemia, the heart is generally affected, in spite of the mitigating effects of the decrease in peripheral resistance (Friedberg). The selective shunting of blood from less important areas to vital organs is also an important compensatory process in the anemic states (Porter et al., 1953).

Cardiac enlargement, one of the main effects of chronic anemia on the cardiovascular system, is partly or completely reversible by specific therapy, as proved by serial roentgenograms.

The reduction in the heart size of these patients depends upon the intensity and duration of the anemic state. In cases of long duration, cardiac enlargement may be persistent, in spite

of appropriate medication, a fact which has been attributed to the occurrence of irreversible hypertrophy.

Figure 16-15 illustrates the decrease in heart size observed in a patient with hookworm anemia following the normalization of the blood count and hemoglobin level as a result of the oral administration of ferrous sulfate.

The mechanism of cardiac enlargement in anemia has not yet been established. The present trend is to consider this type of cardiomegaly as a nutritional deficiency of the myocardium due to chronic hypoxia (Lewis et al.), although one cannot discard the effect of the hemodynamic changes which overload the heart. In favor of this are the clinical observations of Hunter; in his cases, dilatation and hypertrophy did not result from myocardial hypoxemia, since the reduction in heart size occurred in the initial stage of treatment, when the hemoglobin level was still well below normal levels. These cases do not suggest an immediate improvement of the hypoxemic heart but rather the influence of the hemodynamic changes.

The heart sounds are usually altered in anemia. At the apex, the 1st heart sound is generally increased in intensity, and there is a *loud 3d sound*. Murmurs appear frequently, particularly in the severe cases, and may be loud enough to simulate organic valvular disease. *Systolic and diastolic murmurs* may be heard over the entire precordium, particularly in advanced cases of sickle-cell or pernicious anemia. The systolic murmurs are due to rapid circulation, as well as to dilatation of the cardiac chambers and the AV rings. *Diastolic murmurs* are observed in anemic patients in the absence of organic heart disease, simulating either aortic insufficiency or mitral stenosis. They are due to the dilatation of the aortic and pulmonic valvular rings as well as to dilatation of the ventricles (*relative mitral and tricuspid stenosis*).

In addition to these cardiac *murmurs*, a *venous hum* may be heard over the *neck veins* and the *supraclavicular area*.

Nonspecific electrocardiographic changes may be observed, *such as S-T depressions*, low voltage or inversion of the T waves, and, rarely, low voltage of the QRS complex. This will increase in amplitude following appropriate therapy (Figs. 16-16, 17). There is some controversy regarding the frequency and importance of the electrocardiographic changes in chronic anemia. According to a number of publications they occur in approximately 20 per cent of all cases and are usually not marked (Porter et al.; Willius et al.) although they

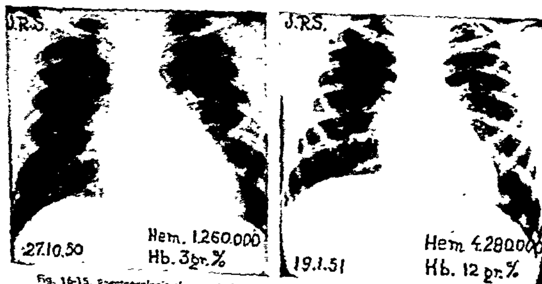


Fig. 16-15. Roentgenologic changes in heart size observed in a 15-year-old patient with severe hookworm anemia. Cardiac enlargement is evident in the initial x-ray film at which time the erythrocyte count was 1,260,000 and the hemoglobin level 3 Gm per cent. Following appropriate therapy there is a marked reduction in heart size, which occurred 3 months later together with a practically normal blood count.

may become more significant in severe cases (Bloch; Carter et al.; Szekely).

Precordial pain has often been described in the literature, and is considered by some as a common manifestation (Lewis; Coombs; Pickering et al.), whereas others (Willius et al.) find this symptom very rarely. Almost every case of anemia complicated by precordial pain has shown pathologic evidence of coronary atherosclerosis (Pickering et al.; Zimmermann; Hochrein; Scherf), and most authors do not believe that anemia per se may cause it. However, Cabot (1926) and Elliot (1934) described cases with perfectly normal coronary arteries.

The fact that appropriate treatment of anemia leads to a rapid and complete relief of the painful episodes indicates that anemia acts as a predisposing factor in patients with organic narrowing of the coronary arteries.

The diagnosis of heart failure in anemia is often difficult since certain symptoms, such as dyspnea, palpitations, and edema, due to the blood dyscrasia may be observed even without heart disease or failure. The presence of tachycardia, heart murmurs, gallop rhythm, and cardiac enlargement may easily mislead and cause the diagnosis of heart failure. The normal venous pressure, and the absence of pulmonary congestion and venous engorgement help in excluding failure. However, severe anemia may lead to both left and right ventricular failure followed by pulmonary and peripheral congestion. In these cases, there usually is associated heart disease but in rare cases anemia may be the sole etiologic factor. One can rule out an associated organic cardiac condition only after disappearance of the anemic state, since the latter may mask or simulate other lesions of the heart

Digitalis has been considered by McMichael as inadequate, and perhaps contraindicated, in heart failure due to anemia, because it decreases venous pressure and consequently cardiac output; however, it has been proved that venous pressure drop is mostly due to increased cardiac efficiency. Therefore, digitalis may be useful and should be given in addition to other therapeutic measures intended to correct the anemic condition. It is important to be er-

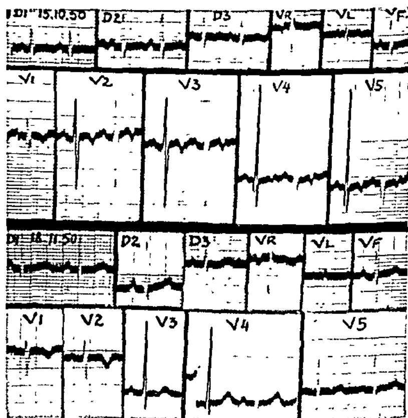


Fig. 16-16. Abnormal electrocardiogram in severe hookworm anemia. The first tracing shows primary T-wave changes and tall R waves in V_4 and V_5 (possible left ventricular dilatation). Following a 30-day period of therapy with ferrous sulfate the tracing became entirely normal.

tremely cautious with blood transfusions, since an abrupt increase in venous pressure may aggravate heart failure and cause acute pulmonary edema. If it becomes necessary to resort to transfusions, they should be given frequently but in small amounts. The prophylactic use of digitalis has been recommended to prevent an unfavorable effect of transfusions.

MALNUTRITION AND STARVATION

The influence of malnutrition and starvation on the cardiovascular system have not been properly emphasized in the medical literature, and it is a current opinion that the heart, contrary to other organs, does not exhibit significant degenerative changes or functional disturbances as a result of starvation. The decrease of body metabolism under these circumstances would tend to reduce the work of the heart by diminishing the cardiac output. As a result of this interpretation, the problems related to the effects of malnutrition did not receive much attention, with the exception of cardiac beriberi, which has been the object of numerous investigations. Lately, however, various factors have led to a modification of the above-mentioned viewpoints, particularly the disastrous effects of surgery in undernourished populations (Weiss), the study of persons liberated from concentration camps (Ellis), and the experiments on normal human volunteers, submitted to inadequate diets with the object of reproducing the poor nutritional conditions occurring in certain parts of Europe during the war (Simonson et al., Keys et al.)

The modern strict dietary treatment of heart failure, hypertension, and myocardial infarction, which involves severe caloric and sodium restrictions, has also led to a reevaluation of these problems, since such treatment may result in unfavorable effects.

According to Keys et al., a prolonged period of undernutrition results in a remarkable metabolic adaptation of the body (decrease of the basal metabolism or reduction of the total energetic metabolism). The former is presumably due to the decrease of body weight as well as the intensity of metabolic changes, whereas the latter results from a diminished activity as well as a more economic type of work. These mechanisms induce a series of compensatory changes in the cardiovascular

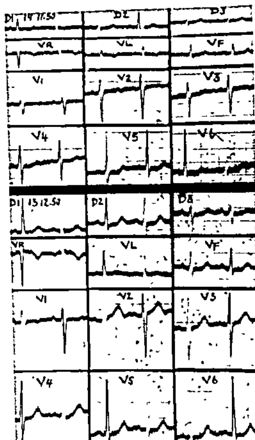


Fig. 16-17. The effects of vitamin B_{12} on the electrocardiographic abnormalities of a patient with pernicious anemia. Primary T-wave changes and low voltage of the QRS complexes are present in the first tracing. One month later the improvement is remarkable, although there is slight depression of the S-T segment in left precordial leads.

system, so that a normal individual may adjust fairly well to the effects of a marked caloric restriction (Weiss et al.).

Among the usual cardiac functional disturbances observed in advanced cases of malnutrition are *bradycardia* and hypotension (Weiss et al.; Keys). The heart rate may fall to less than 50 per minute, and in some cases has been found to be as low as 30. The rhythm is regular; respiratory arrhythmia, as well as tachycardia which normally follows physical exertion, infection, or emotion, disappears. This sign should always be taken into consideration in cachectic patients (Keys). Hypotension is common, with a decrease of systolic pressure and pulse pressure. This is particularly evident in patients with preexisting hypertension (Hellerstein et al.).

The decrease in pulse pressure apparently results from a reduction of cardiac output and stroke volume. These values decrease proportionately more than the degree of reduction in the metabolic changes of the body (Keys). There is a greater utilization of oxygen by the tissues (leading to a lower oxygen content of the venous blood) and a decrease in peripheral blood flow explaining the patient's pallor (which is out of proportion to the degree of anemia), the cold skin, slight cyanosis, and the prolonged circulation time. The venous pressure is often 50 per cent or less of its normal value.

A decrease in heart size, somewhat disproportionate to the degree of weight loss, may be seen in acute and chronic cases of malnutrition, and there usually are microscopic changes in the heart muscle, such as reduction in the size of the myocardial fibers, atrophy, and fatty degeneration (Keys et al.). The concept of cardiac atrophy on the basis of consumptive diseases has been well known for a number of years.

According to Hellerstein et al, *cardiac atrophy* is defined as an acquired reduction in volume and weight of the heart, due to several causative factors, such as neoplastic diseases, chronic infections, and metabolic disorders. The basic nature of the atrophic changes is unknown, but is thought to be the result of a process of autolysis and tissue liquefaction, catalyzed by cellular enzymes (Bradley). This type of atrophy may be observed, not only in normal hearts but in cases of preexistent cardiac hypertrophy, and is reversible following the removal of the causative factor. It is to be emphasized, however, that this reversibility is a slow process, both anatomically and functionally. This must be taken into consideration, in view of the potential dangers of a sudden increase of the metabolic demands, due to excessive food intake, which would lead to an increased cardiac load in the presence of a decreased efficiency of the heart. Under these circumstances, heart failure may occur (Hellerstein et al.; Brozek et al.), as well as complications due to increased blood pressure (Keys; Durant).

Several *electrocardiographic changes* have been described in extremely undernourished individuals (Ellis; Keys; Simonson et al.; Forster), particularly low voltage of all waves. Experimentally, in human volunteers (Simonson et al.) it was possible to observe reduction in amplitude of both atrial and ventricular complexes. The patients were normal young individuals submitted to low-calorie diets for approximately 6 months. Following this period, a high-calorie diet was given and the electrocardiograms returned to normal. A prolongation of the Q-T interval is also frequently observed in such cases, although there is no correlation with the prolongation of ventricular diastole.

During convalescence, in spite of the increase of cardiac rate, the Q-T interval remains above normal limits, and this finding is considered by Simonson et al. as one of the most persistent abnormalities in cases of malnutrition. Displacement of S-T or conduction defects are rare. There is a tendency to right axis deviation, probably due to a change in the anatomical position of the heart as a result of the decrease in size of all organs including the liver and the heart (Keys). The average duration of the above-mentioned ECG changes is from 2 to 3 weeks in the cases studied by Ellis (concentration camp prisoners), whereas the experimental observations of Simonson et al showed that a complete normalization of the tracing occurred only after 32 weeks. It is important to note, that in these cases the electrocardiographic abnormalities often became more marked during the stage of clinical improvement.

There is no satisfactory explanation for the ECG changes which appear in cases of malnutrition and starvation. Vitamin deficiencies do not seem to play a role, since it is a well-known fact that the low vitamin requirements of the hypocaloric diets are rarely conducive to the severe stages of vitamin deficiency. Regarding the electrolytic disturbances, which are undoubtedly present in these patients, the laboratory studies have not been sufficient to prove that they are responsible for the changes. Hypopotassemia and hypocalcemia have been considered, due to the similarity of their electrocardiographic effects. According to Ellis, several factors probably play a role, including protein and carbohydrate deficiencies, and a number of electrolytic disturbances.

The pathologic changes found in the heart in cases of malnutrition are not always sufficiently significant to explain the electrocardiographic abnormalities.

Cardiovascular symptoms are uncommon, even after physical exertion; there is certainly a limitation in cardiac reserve, which does not

cause symptoms following exercise, due to the tendency of these patients to collapse during physical efforts as a result of general muscular weakness.

Orthostatic dizziness and *syncope* are often present as evidence of a marked vasopressor instability. *Peripheral edema* is frequently observed, but it does not seem to be of cardiac origin, since there is no increase in heart size or venous pressure There is, however, a relative increase in circulatory blood volume and extracellular fluids in relation to the body weight The exact pathogenesis of starvation edema remains obscure in many aspects The *low protein content* of the edema fluid is a strong argument against the presence of increased capillary permeability in these cases A marked degree of *hypoproteinemia* must certainly play a role, especially the decrease in serum albumin However, certain objections were raised. Hunger edema has occurred occasionally with normal plasma proteins, and there may be no edema in cases of hypoproteinemia, moreover, the edema may begin to decrease before any change occurs in the plasma proteins. These facts are not sufficient to rule out the influence of hypoproteinemia as a possible cause of edema, since other factors (Friedberg) may also play a role, e.g., variations in tissue pressure, dehydration, and degree of physical activity It is well known that hunger edema may decrease or disappear after rest, and reappear following exertion The increase in venous return as a result of exercise may exceed the capacity of the atrophied heart, and this may cause the edema to appear or become more marked.

It is interesting to note that clear-cut cardiac failure rarely occurs in cases of malnutrition or starvation, even in the presence of long-standing dietary restrictions However, failure may be observed following rapid feeding and a correction of the electrolyte imbalance Under these conditions, dyspnea, tachycardia, venous hypertension, and increase in heart size are observed, as well as the reappearance of edema. This was initially of nutritional origin but its reappearance is caused by congestive failure Although this sequence of events may be caused by disproportion between greater metabolic demands and reduced efficiency of the heart, it is not improbable that other mechanisms may also play a role. Thus, the hypercaloric diets, particularly those due to excessive carbohydrate ingestion, encroach upon the thiamine reserves of the body and may determine a thiamine deficiency which was previously not apparent, thus leading to a typical clinical picture of cardiac beriberi.

The severe hypocaloric diets in the treatment of the advanced forms of hypertension, coronary sclerosis, and other types of cardiovascular disease, are undoubtedly of great benefit to many patients for long periods of time.

However, notwithstanding the immediate beneficial results of such diets, which are either prescribed or forced by special circumstances, *harmful effects may be observed if these restrictions are imposed for long periods of time* and may greatly overshadow the initial favorable effects. *A similar mechanism occurs in chronic constrictive pericarditis and in organic tricuspid valvular disease complicated by hypoproteinemia, notwithstanding an adequate diet.* Under these circumstances, one of the most serious effects is *hypoproteinemia*, which is increased by repeated removal of ascitic fluid. Actually, heart failure per se predisposes to a decrease in plasma proteins through various mechanisms including chronic congestion of the liver, leading to hepatic insufficiency and hepatic cirrhosis *Albuminuria*, which commonly occurs in heart failure, may contribute to the protein deficiency. Thus, it is not surprising that hypoproteinemia should occur in chronic heart failure with a decrease in serum albumin and a reduction in the albumin/globulin ratio In cases of marked protein deficiency, this may contribute to maintain the edema and, in many instances, explains the apparent irreversibility of these changes (Durant).

It is to be emphasized that the low-calorie diets lead to a greater utilization of the ingested proteins, which are used for energetic changes rather than for the nitrogen balance of the body (Stare et al.). Thus, an adequate protein intake in a low-calorie diet may prove to be relatively inadequate, whereas, in a normal diet, the protein requirements are lower

PELLAGRA

Electrocardiographic changes which closely resemble those observed in beriberi have been described in pellagra (Feil, Mainzer et al, 1946, Mainzer, 1948; Porter et al; Rachmile-

witz et al., 1944, 1945) and were initially interpreted as probably due to an associated thiamine deficiency. Mainzer and Krause (1946) described these changes in 23 cases of pellagra, some of whom reverted to normal following the administration of nicotinic acid; however, these authors did not mention the thiamine content of the hospital diet. Subsequently, Mainzer described the results of a study of 45 cases of pellagra and concluded that, although nicotinic acid deficiency may be the sole cause of the ECG changes in some cases, it was necessary to give thiamine supplements to others in order to obtain a complete normalization of the ECG.

According to Rachmilewitz and Braun (1945a), the ECG changes were seen in only some instances, all of which showed visceral involvement due to this type of avitaminosis. The main ECG abnormalities described were primary T-wave changes and S-T segment depression, all of which rapidly disappeared following administration of nicotinic acid, while they remained unchanged by thiamine treatment. It is interesting to note that, in two cases, the response to nicotinic acid was noted only after the control of an associated hypoproteinemia In the remaining nine cases, all of which exhibited the cutaneous form of the disease as their sole clinical manifestation, significant electrocardiographic abnormalities were not observed. The authors concluded that, notwithstanding the similarity of the ECG pictures, cardiac involvement in pellagra differs considerably from that of beriberi, especially in view of the absence of cardiac enlargement or evidence of heart failure. In patients with ascites and peripheral edema, hypoproteinemia was the main factor responsible.

The authors had the opportunity of studying nine cases of pellagra, three of which were associated with beriberi heart disease In the latter, it was impossible to evaluate the influence of nicotinic acid deficiency on the electrocardiographic changes However, in the six cases of uncomplicated cutaneous pellagra, the authors did not observe any type of electrocardiographic abnormality.

VITAMIN C DEFICIENCY

The lack of ascorbic acid has been pointed out as a cause of cardiac involvement in a number of experimental studies; it has been suggested as a possible factor in the pathogenesis of rheumatic fever. These observations have not been confirmed clinically, since the few instances of cardiac enlargement described in cases of scurvy were not sufficiently analyzed to rule out the possibility of an associated beriberi heart disease.

BERIBERI

A deficiency in vitamin B_1 plays an important role in cardiovascular pathology as the cause of an unusual type of heart disease which is completely reversible provided it is recognized and adequately treated in its early stages. The incidence of this type of cardiac disease has been generally underestimated. The authors believe that it is not a rare condition, since in the last 4 years they have identified no less than 63 cases of beriberi heart disease, in addition to a number of others in which thiamine deficiency played a secondary role in the course of other types of cardiac disease.

The initial observations of this condition were among the Oriental populations, as a result of dietary deficiencies (Aalsmeer et al.; Wenckebach; Keefer; Shimazono), whereas in the Western Hemisphere, most cases are due to chronic alcoholism (Weiss et al; Weiss; Goodhart et al.). This fact was brought out in the authors' observations, since all their patients, without exception, were chronic alcoholics (Benchimol, 1953; Benchimol et al, 1947, 1951, 1953). It is interesting to note that most cases of vitamin deficiencies do not occur in extremely undernourished patients, but rather in those with a high caloric intake resulting in a normal or excessive body weight. This is explained by the higher vitamin requirements of the hypercaloric diets. Carbohydrates require thiamine for their complete metabolism (Lecocq). It is well known that vitamin B_1 participates in carbohydrate metabolism as a coenzyme (cocarboxylase). (See Part 2, Chap. 31.)

Since the *polished rice diet* of the Orient and chronic alcoholism in the Western Hemisphere both represent essentially a high-carbohydrate and a low-thiamine intake, it is obvious that under either circumstance a vitamin B_1 deficiency may result, leading to beriberi heart disease. This is particularly true of chronic alcoholics having a diminished appetite and

an associated gastrointestinal disturbance which decrease the absorption of thiamine.

An interesting feature of this *condition* is that most patients are apparently well nourished, and some of them are actually *obese*. This is accounted for by the high caloric content of their diets, notwithstanding the above qualitative deficiencies

Since chronic alcoholism is so much more frequent than cardiac beriberi, it is probable that other associated factors play a role, such as physical exertion, infections, thyrotoxicosis, or pregnancy. The direct effect of alcohol on the heart muscle, leading to an "alcoholic myocarditis," *is no longer accepted as an explanation* for beriberi heart disease The clinical *manifestations in these* patients have been seen to disappear following the administration of high doses of thiamine, notwithstanding a continued alcoholic intake (Weiss) It is believed that chronic alcoholism *affects the cardiovascular system* as a result of thiamine deficiency, although it *is difficult to* say whether myocardial failure occurs as a result of interference with energy production or because of increased cardiac work resulting from the possible vasodilator effect of pyruvate (Best).

The *clinical picture* of beriberi heart disease is not confined to the classical descriptions of this *condition in* the Orient, i.e., a disorder having as its main features rapid circulation *associated* with *right* heart failure. Most cases studied in this hemisphere *do not* exhibit the hyperkinetic syndrome and often show evidence of left heart failure. Peripheral edema is one of the *earliest and most important signs* which has been observed in every patient in the authors' series, either as the *sole initial* manifestation or associated with exertional dyspnea *Signs of pulmonary congestion were* often present. *Apical systolic murmurs* (grade 1 or 2) were common and are probably due to relative mitral insufficiency.

In certain cases, a transient *diastolic murmur* was *present* which simulated aortic insufficiency. *Gallop rhythm* was a frequent finding

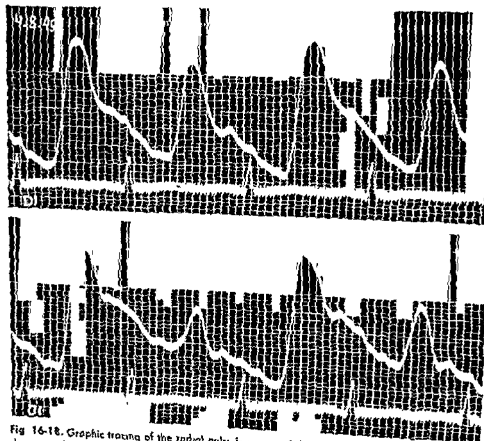


Fig 16-18. Graphic tracing of the *radial pulse* in a case of *decompensated beriberi heart disease*, showing pulsus alternans *(above)*, which is accentuated by the *Valsalva maneuver* (below).

and disappeared following recovery. An interesting feature was the lability of the heart rate, a transient and rather marked bradycardia appeared either during heart failure or in the stage of clinical improvement. *Pulsus alternans* was observed in two patients, and it was interesting to note that it occurred during clinical improvement and shortly before hospital discharge (Fig. 16-18). The *lability of blood pressure* is also typical. In certain cases, there is an *increase in pulse pressure;* in others on the contrary, there is a diastolic hypertension during the stage of congestive failure, which may persist for some time after recovery.

In one-third of the cases there may be evidence of *rapid circulation*, such as decreased circulation time; however, few cases exhibit a typical hyperkinetic syndrome with increased pulse pressure, water-hammer pulse, normal circulation time in spite of the congestive heart failure, and exaggerated cardiac pulsations at fluoroscopy.

The presence of *polyneuritis* is additional evidence of thiamine deficiency and is seldom absent.

These clinical manifestations are usually sufficient to identify beriberi heart disease, particularly in cases of chronic alcoholism However, the course of changes of the clinical picture after administration of thiamine is the most valuable diagnostic criterion.

The *roentgenologic examination* of the heart in beriberi heart disease does not show a characteristic configuration, however, a decrease in heart size following thiamine treatment is important for diagnosis. Cardiac enlargement occurs in the majority of cases with or without evidence of pulmonary congestion Either right or left chamber enlargement may predominate while diffuse dilatation occurs in some instances (Figs. 16-19, 20). Most patients exhibit a predominant enlargement of the left ventricle. The prominence of the left middle arch, observed in some cases, may simulate mitral heart disease When pulmonary congestion occurs, it is predominant in the hilar regions. The cardiac enlargement is not always rapidly and completely reversible. Depending upon the intensity and duration of the myocardial lesions, the condition may be only partially reversible or even completely irreversible. This is explained by the fact that interstitial edema and degeneration of the myocardium may lead to myocardial fibrosis which then may simulate other degenerative conditions such as coronary heart disease (Schlesinger et al.).

The *electrocardiogram* frequently reveals several abnormalities due to myocardial in-

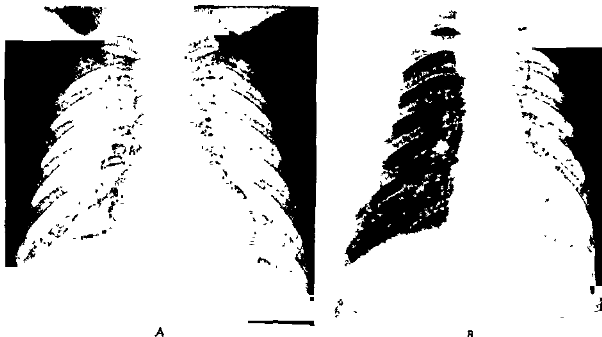


Fig. 16-19. A. The initial x-ray film reveals cardiac enlargement involving both the left and the right heart chambers. B. Two weeks later the roentgenogram has become normal.





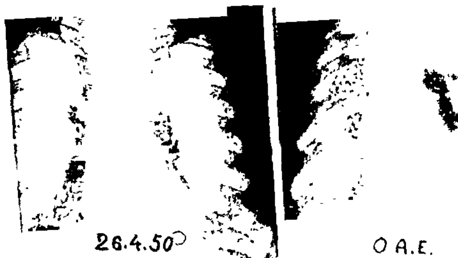


Fig. 16-20. Serial roentgenograms. Thirty-eight-year-old *chronic alcoholic*, admitted in advanced heart failure. The first x-ray film shows a considerable increase in heart size as seen in PA and LAO positions, in addition to slight dilatation of the aorta, and hilar congestion. Following intravenous thiamine therapy, the cardiac shadow is markedly decreased 1 week later, and subsequently becomes completely normal.

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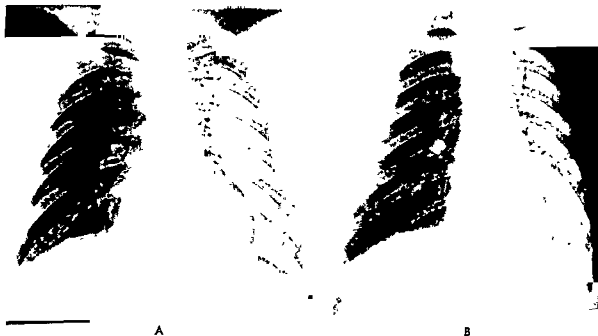


Fig. 16-19. A. The initial x-ray film reveals cardiac enlargement involving both the left and the right heart chambers. **B.** Two weeks later the roentgenogram has become normal.

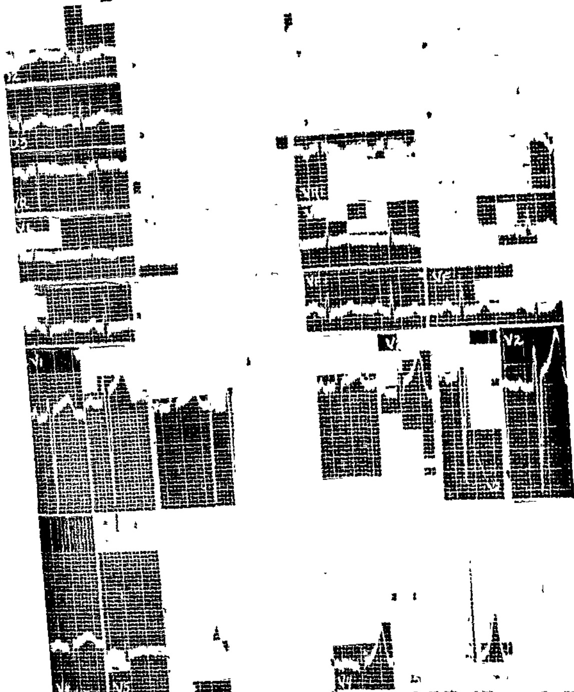


Fig 16-22. A 41-year-old man with beriberi heart disease, showing initial T-wave inversion in leads I and aVL and diphasic deflection in lead V_5, in addition to signs of moderate left ventricular hypertrophy. Nine days later, these changes have become less marked, and they disappear completely in the third tracing The last electrocardiogram, recorded when the patient was fully compensated, exhibits an increase in voltage of the T waves as compared to the previous tracing

volvement. Although these changes are not specific, their disappearance following the administration of thiamine is of importance in the diagnosis and evaluation of the clinical course of these cases. Low or inverted T waves are often present, either as an isolated finding, or associated with low voltage of the QRS complexes (Fig. 16-21). In the course of clinical improvement, the T waves may become tall and peaked, possibly on account of the predominant tonus of the vagus nerve not uncommonly found in such cases. These abnormalities are not always reversible for the same reasons which were discussed in regard to the roentgenologic findings The T wave may be inverted from the outset (Fig. 16-22) and become progressively normal as the clinical picture improves, or, on the other hand, it may become more inverted during the stage of recovery from heart failure (Fig. 16-23). Disturbances in rate and conduction are not generally described. However the authors have

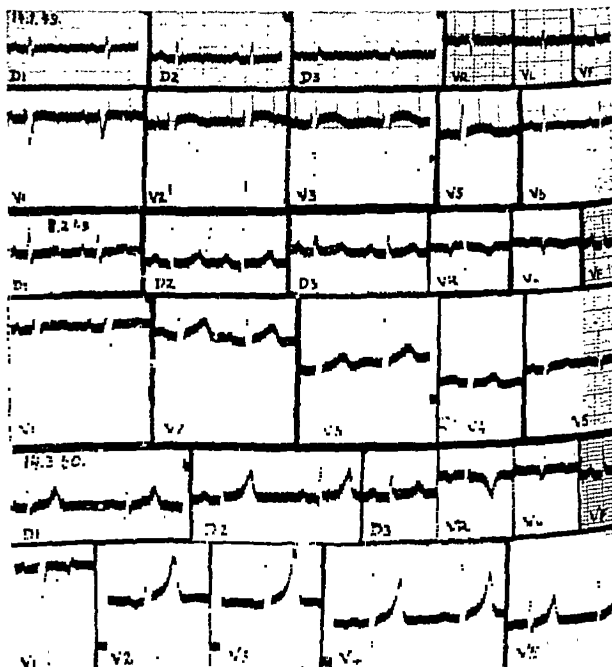


Fig. 16-21. Progressive improvement of electrocardiographic abnormalities in a 42-year-old man in *heart failure due to thiamine deficiency*. The first tracing shows low voltage of the QRS complexes and flat T waves. Three weeks later, there is an increase in amplitude of all deflections. The third ECG shows tall, peaked T waves in the standard and precordial leads.

observed a case of first-degree AV block and also a case of left bundle branch block confirmed on necropsy (Schlesinger et al). Electrocardiographic signs of left ventricular preponderance may be found and are probably explained by dilatation because they are often partly or completely reversible. This may raise the problem of differential diagnosis with hypertensive heart disease. The enlargement of the heart is occasionally reversible while the ECG changes may persist in spite of adequate treatment (Fig 16-24).

The *diagnosis* of beriberi heart disease is relatively simple in the presence of the syndrome of high output failure. However, rapid circulation may be absent and there may be left ventricular failure Then, diagnosis may be more difficult because the clinical picture resembles that caused by other types of heart disease of other origins.

Certain diagnostic features are important:

1. History of chronic alcoholism
2. The presence of other manifestations of vitamin deficiency, such as polyneuritis
3. The absence of other causative factors of heart disease
4. The favorable effects of rest and thiamine administration

The course and prognosis depend upon the intensity and duration of myocardial involvement, since the long-standing effects of thiamine deficiency may lead to an irreversible type of cardiac disease. The presence of an associated form of heart disease is an unfavorable feature, and explains why at times it may be difficult to achieve complete recovery with the usual doses of thiamine.

Certain cases, exhibiting an acute onset, were described in the Orient as *shoshin* or the "acute pernicious form" of beriberi. Patients with shoshin present sudden onset of severe heart failure with cyanosis, precordial distress, and shock, which often ends fatally after a short period. Such cases must be immediately recognized since a dramatic improvement often ensues following the intravenous administration of thiamine.

The failure of favorable response to thiamine therapy does not necessarily rule out the diagnosis of beriberi in any case of heart disease, as several authors have repeatedly emphasized (Alleman et al; Blankenhorn, 1948; Blankenhorn et al, 1946; Vilter).

The authors' observations indicate that beriberi heart disease under certain conditions is followed by diffuse myocardial fibrosis, with electrocardiographic changes which closely resemble those caused by chronic coronary insufficiency or other types of myocardial disease.

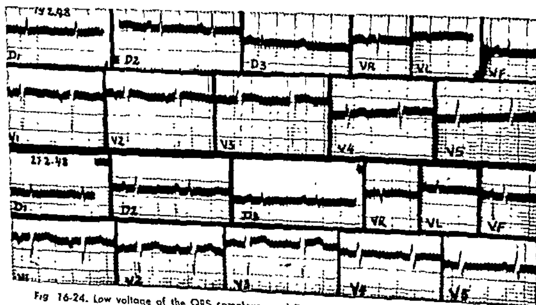


Fig 16-24. Low voltage of the QRS complexes and T waves of a 33-year-old patient with irreversible beriberi heart disease. Notwithstanding thiamine therapy, there was no clinical response, and the second tracing, taken one week later, remained unchanged The diagnosis of this case was confirmed by post-mortem examination.

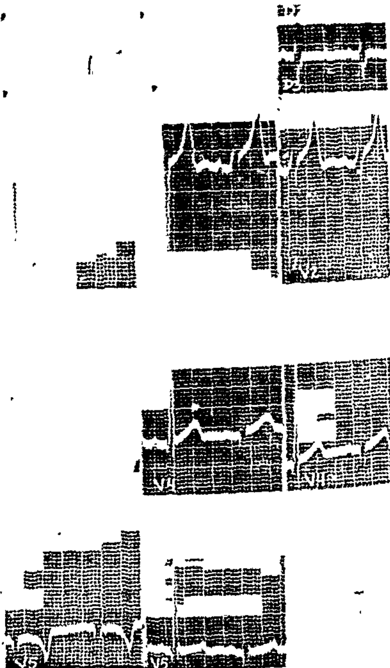


Fig. 16-23. Serial electrocardiograms of a 38-year-old *chronic alcoholic* (male) in heart failure. The initial tracing shows *primary T-wave* changes with evidence of left ventricular hypertrophy. The second electrocardiogram, *recorded* 20 days later, during clinical improvement, reveals an accentuation of the T-wave changes with inversion of this deflection which becomes more marked on *6/28/1949*, in addition to an *increase* in voltage of the R waves in leads V_4 and V_5. The subsequent electrocardiograms show *progressive* improvement of the T-wave abnormalities. In the last tracing, these deflections have become normal and upright, although there are persistent signs of left ventricular hypertrophy.

the authors do not believe in the routine use of digitalis in beriberi heart disease, this drug may be given, not only in cases of associated heart disease, but also when there is a diagnostic problem and the administration of thiamine is not rapidly effective. This procedure seems especially justified in cases of severe heart failure, in which all available measures should be attempted It should also be emphasized that bed rest alone is often beneficial, although most patients require the administration of thiamine

Thiamine should be given initially by the intravenous or intramuscular route, in order to obtain the maximal results. This may be followed by the oral administration of a maintenance dose. The daily dose of 100 mg is probably excessive, however, since unfavorable results have never been observed even with massive doses (Weiss et al), this dosage seems justified, particularly in view of the fact that it is difficult to judge the requirements of individual patients

The use of other components of the vitamin B complex has been advocated since associated vitamin deficiencies often occur. However, in the initial stages, the authors prefer the administration of thiamine alone in order to observe its specific effects, adding the other vitamin fractions later if necessary. Obviously, the control of chronic alcoholism and the correction of the dietary deficiencies should be carefully completed, and full instructions given to the patients Unfortunately, however, they often tend to revert to their previous habits, once they have obtained considerable relief from the signs and symptoms of beriberi heart disease

CIRCULATION TIME IN BERIBERI AND IN ANEMIA

BERIBERI HEART DISEASE

The cardiovascular dynamics of beriberi have their origin in the peripheral vascular system and consequently resemble the mechanisms encountered in anemia, hyperthyroidism, ar-

and to consequent peripheral vasodilatation The abnormal peripheral *circulation is due* to deficiency of thiamine and to *faulty oxidative* mechanisms mediated through the enzyme cocarboxylase There is also some experimental evidence that the lack of thiamine has a direct action upon the myocardium as well as upon the periphery. In such cases, *the circulation* time becomes accelerated as the peripheral resistance becomes diminished through the multiple arteriovenous shunts As in *other* conditions associated with an abbreviated circulation *time*, beriberi heart is characterized by an increase in the venous return *as well* as by an increase in the cardiac *output* According to various investigators, the circulation time is not increased in all cases Keefer found it increased in only about one-third of the cases he observed in China. *Blankenhorn* et al stressed that, in the Western type of beriberi, the acceleration of circulation time is rare According to the literature, when heart failure supervenes in beriberi heart, the data relating to circulation times may be obscured, not *only by heart failure*, but also by mental cloudiness, which renders accurate evaluation more difficult

ANEMIA

Since the pioneer observations of Blumgart et al with radium C, it has been known that circulation time is reduced in both primary and secondary anemias and that the increase in circulation speed parallels the severity of *the anemia*. In a general way, it has been found that a reduction in hemoglobin between 6 and 8 Gm will give circulation time measurements which are comparable to those obtained in arteriovenous fistula, hyperthyroidism, beriberi, pregnancy, and febrile states. Although the circulation speed does not become noticeably altered until the hemoglobin falls to a level of *less* than 8 Gm, reductions in hemoglobin below 6 Gm have pronounced *effects* in accelerating blood flow. *In such* cases, it has not been unusual to obtain an "arm-to-tongue" time of 6 *sec*. Apparently the quantity of blood reaching the tissues may be doubled or more by *virtue* of an accelerated blood flow which a *priori* increases the cardiac output In this way, the body tissues can withdraw as much *oxygen* per unit of time as they would if the hemoglobin content *of the blood*

From the *pathogenic standpoint,* Aalsmeer and Wenckebach believe that a metabolic disturbance resulting from thiamine deficiency causes fluid retention leading to edema of the striated muscles, including the myocardium itself, and decreasing cardiac contractility. According to them, there is no hypertrophy of the heart in beriberi, but rather an increase in thickness of the ventricular walls due to edema of the myocardium. Notwithstanding the diffuse involvement of the heart, they observed an initial and predominant right heart failure and the early occurrence of tricuspid insufficiency due to right ventricular distention. Several cases exhibit peripheral arteriolar dilatation, partly attributed to vasomotor paralysis and partly to acidosis, as a result of accumulation of lactic acid in the blood, a finding which becomes more marked on exertion (Inawashiro et al). In view of this hemodynamic disturbance, there is an overload of the right ventricle which is already involved by the above factors.

Although the exact mechanism of heart failure in beriberi is not entirely understood, the available evidence points to the combined result of myocardial damage and peripheral dilatation, leading to a peculiar combination of an overactive circulation and a failing heart.

The importance of the vascular factor was emphasized by Wenckebach, who described the vascular syndrome of Oriental beriberi Youmans and Huckins attributed the early cardiovascular changes to a "chronic venous congestion without heart failure." This syndrome is characterized essentially by hypervolemia with increased venous pressure and other congestive manifestations, due to a diffuse vasodilatation, increased venous return, and elevated cardiac output.

Since the arteriolar changes are less marked in the kidneys, there is a relative renal ischemia, which presumably persists until it is neutralized by the increase in cardiac output. According to these authors, it is possible that the renal factor may be involved in the mechanisms which lead to hypervolemia. These hemodynamic changes become more marked and persistent, resulting eventually in cardiac strain by stretching the myocardial fibers to a point which interferes with their adequate contractility, this is the main cause of heart failure with a decrease in cardiac output, as compared to its previously normal levels. According to these studies, it is important from the therapeutic standpoint to distinguish the hemodynamic phase from the myocardial stage of beriberi heart disease. Digitalis is not recommended in the former while it may be useful in the latter.

The importance of the vascular factor is recognized by most authors, such as Weiss and Wilkins (1937a). The authors believe that it is not as important as it has been claimed in the Orient, since they have observed the hyperkinetic syndrome in less than 50 per cent of their own cases. They believe that, in most cases, the myocardial lesion was mainly responsible for the cardiovascular changes and represented the sole factor leading to heart failure.

Thus, two factors are involved in variable degrees in the pathogenesis of heart failure in beriberi. For some unknown reason, the peripheral vascular changes predominate in the Orient, whereas the myocardial factor is more important in the Occidental form of cardiac beriberi.

In summary, thiamine deficiency results from the disproportion between the ingestion of vitamin B_1 and the caloric content of the diet, it leads to a disturbance of the intermediary metabolism of carbohydrates with an increase in the blood levels of lactic and pyruvic acids affecting the heart muscle. A certain degree of peripheral vascular dilatation which results from either an accumulation of the acid metabolites or a degenerative process of the perivascular nerve endings, leads to an increase in venous return. The combined effect, of cardiac overload and myocardial involvement, culminates in the clinical picture of high output failure.

Therapy. The administration of thiamine is obviously the basis of therapy. A dramatic improvement of heart failure often occurs in advanced cases which do not respond satisfactorily to cardiac glycosides. In view of these results, the therapeutic test with thiamine has been included as one of the important diagnostic criteria in beriberi heart disease. Although of great value, it should be emphasized that it may occasionally fail in the severe and irreversible forms of the disease, while digitalis and diuretics may induce remarkable improvement

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Endomyocardial fibrosis

Pathological Aspects

J. N. P. DAVIES

Clinical Aspects

A. W. WILLIAMS

Cardiac Catheterization in Subendocardial Fibroelastosis and Constrictive Diseases

JOSHUA LYNFIELD AND BENJAMIN CASUL

PATHOLOGICAL ASPECTS

Fibrotic thickening of the endocardium is seen in a variety of conditions It is a very marked feature in endocardial fibroelastosis, which is known to affect adults as well as children Fibrosis of the endocardium is often found over old areas of myocardial damage, as in ischemic heart disease, or in areas contiguous to valves which are the sites of rheumatic or arteriosclerotic changes, it is also found in areas where blood eddies or abnormally directed blood streams impinge on the endocardial surface and cause the so-called *Zahn-Schmincke pockets to develop* Endocardial fibrosis is a feature of certain types of congenital heart disease and is especially marked in the left ventricle of those patients in whom the left coronary artery arises from the pulmonary artery Apart from these well-defined conditions, there are many reports of patients who have died with intractable heart disease and who have been found at autopsy to have varying degrees of endocardial fibrosis, multiple mural thrombi, or both These have been recorded, either as isolated cases or as small groups from most European countries and from North America over a period of many years The origin of these cases remains obscure, the pathogenesis uncertain, and the classification unsatisfactory. This is reflected in the profusion of names applied to these conditions: subacute, isolated, idiopathic, or pernicious myocarditis; parietal endocardial sclerosis, cardiovascular collagenosis; nutritional heart disease; Occidental beriberi, chronic parietal endocarditis of nonvalvular origin, recurrent parietal thromboendocarditis, endocarditis parietalis fibroplastica, and so on One condition has been more clearly defined, namely, *Löffler's disease* or *endocarditis parietalis fibroplastica* in which there is usually a marked blood eosinophilia, which may or may not persist until death Apart from the eosinophilia, other evidence of allergic states has been found in a number of cases described under this name, and in some patients a definite valvulitis has been seen.

In recent years many cases of heart failure with endocardial fibrosis have been found in different parts of Africa and it is now clearly recognized as a major cause of heart disease in Africans in several areas of Africa. The frequency of this disease was first recognized in African troops in Egypt in World War II. The high incidence in Uganda was first realized in 1946, and subsequent reports have shown that it exists in the Sudan, Belgian Congo, Nigeria, Ghana, and in Gambia, as well as in Central Africa. It seems to occur less rarely in South

were normal, a fact corroborated by plethysmographic studies which reveal that the quantitative increase of blood flow through peripheral tissues in the presence of anemia is considerable.

Peripheral mechanisms operate to increase the circulation speed in chronic anemia. The impoverished blood leads to tissue *hypoxia* which results in the accumulation of acid metabolites. The direct or reflex action of the latter is responsible for peripheral vasodilatation. A more rapid venous return to the heart ensues, through a mechanism which is strongly *suggestive of the presence of multiple peripheral venous shunts*. There also is an additional factor of diminished viscosity engendered through the presence of a low red-blood-cell count.

When heart failure complicates *severe chronic anemia*, it fails to produce the characteristic prolongation of circulation time. If it is pure anemic heart failure with a very low hemoglobin content, the circulation time may, in fact, be within the normal range. This is due to the fact that, although congestive heart failure causes slowing of the circulation speed, the retardation is in part neutralized by the diminished blood viscosity in anemia, by the increased cardiac output, and by peripheral *vasodilatation*. Thus, circulation time reading will depend, not only upon the degree of heart failure, but also upon the degree of anemia.

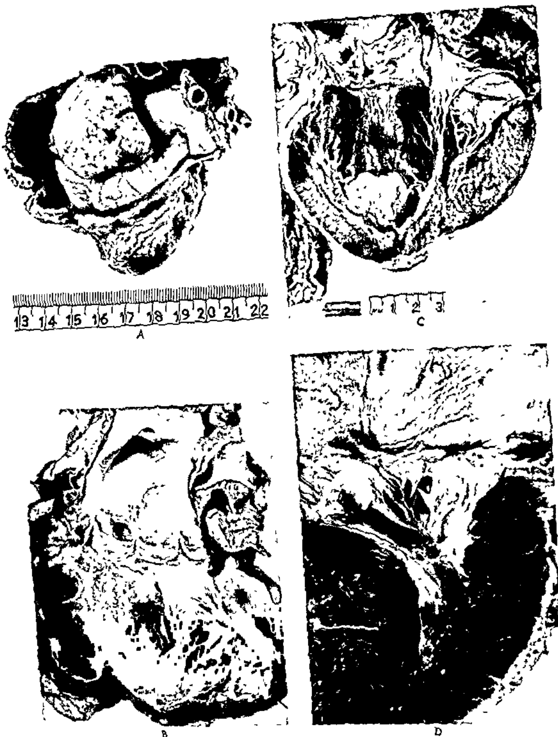


Fig. 16-25. Upper left: external view of heart of a case of endomyocardial fibrosis with lesions in the right ventricle, showing the external depression. Upper right: Left ventricle in a case of endomyocardial fibrosis showing noninvolvement of the endocardial tissue below the aortic valve and mitral valves. Lower left: Left ventricle in a case of endomyocardial fibrosis showing involvement of the myocardium of the apex and inflow tract extending behind the mitral valve. Lower right: Involvement of the mitral valve, which is being bound down to the mural endocardium, in a case of endomyocardial fibrosis.

Africa. There are indications that it occurs in India, Oceania, and Malaya, as well as in the West Indies and South America.

The name *endomyocardial fibrosis* has been given to this condition, first to emphasize the dual involvement of the endocardium and the myocardium, second because it was at first found only in Africa, and third because the lesions appeared, and still appear, to differ in many respects from those reported in the conditions previously mentioned. Thick irregular plaques of fibrous tissue cover parts of the endocardial surfaces of the cardiac ventricles and atria. The ventricular endocardium of the inflow tract and apex are particularly affected, and the atrioventricular valves are frequently involved in the fibrotic process, although the latter never involves the semilunar valves. Mural thrombi are often superimposed on the fibrous tissue, and strands of fibrous tissue invariably extend deeply into the myocardium Elastosis is not a feature of this condition.

Incidence. In Southern Uganda, recently, endomyocardial fibrosis has been the form of heart disease most frequently diagnosed in African patients (21 per cent of cases with heart disease). This is of course in a population in which coronary heart disease, thyrotoxic heart failure, and pulmonary heart disease are extremely rare, and in which subacute bacterial endocarditis, severe atheromatosis, and malignant hypertension are uncommon. On the other hand, infectious forms of heart disease and hypertension secondary to renal disease are common The clinical evidence is supported by autopsy data which showed that endomyocardial fibrosis was found in 33 instances, out of 231 autopsies on patients dying of heart disease. It affects both sexes equally and occurs at all ages, from 40 months to over 70 years.

Pathological Changes. The affected heart may vary from *hypertrophic* to *grossly atrophic,* weights of from 120 to over 600 Gm having been recorded in African adults The normal heart weight of the Uganda African is 0 58 per cent of the body weight but, since the body weights of Africans are considerably lower than those of European adults, the heart weights in absolute figures tend to be lower. Allowing for this, *cardiac hypertrophy* is found in about 60 per cent of cases. Large *pericardial effusions* are sometimes seen Externally, the heart often shows a rugose wrinkled appearance of the epicardium, particularly towards the apex. Over *the apex of the right ventricle,* there may be a deeply depressed, puckered area forming a saucerlike or wedge-shaped depression (Fig 16-25A). Occasionally such a depression is seen above the apex (small-waisted right ventricle). These external depressions are not seen over the left ventricular apex; when seen over the right apex, they indicate that a severe lesion is present in the right ventricle. About half of the cases of endomyocardial fibrosis show these depressions and in some instances there is an accompanying dilatation of the pulmonary conus.

Internally, the endocardium of the ventricles shows the most constant and severe lesions While only one ventricle may be affected (Fig. 16-25B), in the majority of cases lesions are present in both, though the most extensive and severe lesions are usually found in the left ventricle. Lesions of the atria are present in about one-third to one-half of the cases, either in the form of an adherent ante mortem thrombus or of fibrosis of the endocardium, patchy or diffuse. The lesions of the ventricles follow a definite pattern. The apex of the ventricles is most commonly involved with the lesion extending only a short distance up the septal wall, usually for about one inch, and terminating in many cases in a thick ridge of fibrous tissue with a rolled edge Above this, in the left ventricle, the endocardium is invariably unaffected below the aortic valve (Fig. 16-25C). Spread of the lesions onto the anterior wall is usually restricted in a similar manner but, in striking contrast, the posterior walls are extensively involved, with thick masses of fibrous tissue extending upwards and reaching to the base of the posterior cusps of the atrioventricular valves. Thus, a thick layer of fibrous tissue often extends downwards, from behind the posterior cusps of the AV valves, over the whole of the posterior wall and over the whole apex of the left ventricle, to form a single sheet of fibrous tissue of a shape not unlike an old-fashioned wax-candle snuffer. To this sheet of fibrous tissue, which lies behind the posterior cusps, the valve cusp itself may become adherent together with the chordae tendineae and papillary muscles, so that the

the regions penetrated by the fibrous tissue strands is normal in gross appearance or may appear slightly engorged, but myocardial fibrosis not connected with the endocardial fibrosis is not seen No lesions have been noted in the coronary arteries or veins or in the cardiac nerves or lymphatics, and the epicardial and pericardial surfaces usually show no lesions, even though sizable pericardial effusions may be seen

In summary, the gross lesions of endomyocardial fibrosis consist of *apical and inflow tract endocardial fibrosis* with involvement of the inner parts of the myocardium, there is often a superimposed mural thrombus, sometimes calcification, and rarely a terminal bacterial endocarditis. Fibrosis with thrombus formation occurs in the atria The posterior cusps of the atrioventricular valves are often bound down to the mural fibrous tissue and, in severe cases, the whole of the valvular apparatus may disappear The other AV valve cusps are less frequently involved and the semilunar valves are unaffected Associated congenital lesions are very rarely encountered.

Histological examination adds comparatively little to the knowledge gained by gross examination The fibrous tissue is compact and often hyalinized in the superficial areas and more loosely textured in the deeper layers where there are usually many thin-walled dilated blood vessels with a sprinkling of chronic inflammatory cells in which some pigmented macrophages may be seen Dilated blood vessels, all thin walled, are seen in the strands of fibrous tissue penetrating into the myocardium and these are presumably dilated thebesian veins and arterioluminal vessels There is usually no elastic fiber production and, where elastosis does occur, it is scanty and irregular. Calcification, where present, is seen in the more compact superficial layers of the fibrous tissue or in the affected valve cusps

The myocardium is constantly invaded by the strands of fibrous tissue in which are the blood lagoons, and these strands tend to surround small areas of myocardium in which a variety of degenerative changes may be observed In other areas, including those not covered by endocardial fibrosis, the myocardial fibers usually show degenerative changes Commonly these consist of a watery vacuolization or an interfibrillary edema, producing the aptly named *moth-eaten fibers* The nuclei are often large and hyperchromatic with square ends or may be shaped like long cigars Fatty infiltration is not seen. The changes are most marked in the subendocardial regions and diminish in intensity toward the deeper layers Cellular infiltration is always minimal; Aschoff bodies are not seen; and the only increased cellularity seen is in the layer of chronic inflammatory cells of the granulation tissue layer separating the fibrous tissue from the myocardial fibers. There has been no evidence of parasitic disease, and old or recent large scale necrosis of cells is not seen, save in some of the small areas surrounded by fibrous tissue Where the fibrotic lesions are advanced, there may be obliterative changes in some of the smaller arteries, but this is seen only in a minority of cases

No constant gross or microscopic changes are seen in organs or tissues other than the heart. Death is often from pneumonia or some other infective condition Examination has failed to reveal evidence of any generalized vascular disease or occlusive condition, or of any allergic lesions or generalized collagenous change. A puzzling feature is the existence of patients who show no evidence of cardiac disease in life but, after death from some unrelated disease, may show severe endomyocardial fibrosis It is thus evident that severe degrees of endomyocardial fibrosis may exist, particularly if the heart valves are not affected, without causing obvious embarrassment to the cardiac action Eosinophilia in the blood or in the tissues is not a feature of these cases and occurs only in a minority of instances.

CLINICOPATHOLOGICAL CORRELATIONS

The differences in the gross lesions found in hearts affected by endomyocardial fibrosis can be correlated with various clinical patterns which are encountered in patients with this disease There may be no clinical evidence of heart disease in some, as described above There may be evidence of failure of one or other or both ventricles with or without evidence of disease of the atrioventricular valves Some patients present evidence of constrictive heart disease. Where valvular disease exists, it usually takes the form of incompetence of the mitral, or, less commonly, the tricuspid valve. Stenosis of these valves may occur but

cusp itself disappears in a single sheet of irregular fibrous tissue extending from the atrium to the apex (Fig. 16-25D). The outlines of the engulfed chordae tendineae and the papillary muscles may be appreciated as irregular ridges in the sheet of fibrous tissue, and the outline of the cusp may be felt as a firm ridge.

While this is the basic type of lesion seen in advanced cases in the ventricles, in the right ventricle it is often modified by changes due to the peculiar configuration of this chamber. The spatial arrangements are such that, when the fibrous sheets form, the surfaces rapidly come into contact with each other and fuse. As a result, the whole apex is filled with fibrous tissue and thrombus, and the cavity of the apex is obliterated. When the cavity is filled at the apex, a section of the ventricle at right angles to the septal wall will disclose a triangular mass of clot and fibrous tissue. However, the fusion may take place at some distance above the apex, when this happens, the cavity below falls in, and a large triangular wedge of muscle is seen on sectioning at a right angle to the septal wall. In such instances, a small endocardium-lined crypt may be found in this wedge of muscle, indicating the original apical cavity of the right ventricle. However the obliteration of the right ventricle comes about, it is always manifested externally by the puckering and depressions over the right ventricle previously described, and the presence of such an external lesion is a sure indication of obliteration of the cavity. The effect of this obliteration is to move the effective apex of the right ventricle progressively nearer to the tricuspid valve while the available cavity of the right ventricle is reduced to a shallow saucer in which the fibrosed posterior papillary muscle frequently sticks up like a marble pillar In such cases, the pulmonary conus is usually dilated and hypertrophied and there may be some fibrosis of the endocardium. This, however, is always slight and always ends some distance below the pulmonary valve cusps Like the cusps of the aortic valve, the pulmonary cusps have not been affected, in over 100 cases of endomyocardial fibrosis examined However, some of the longest clinical histories of heart disease are given by patients who are found at autopsy to have right ventricular obliteration and a dilated conus with hypertrophied muscle.

Obliteration of the apex has not been found in the left ventricle, but the largest mural thrombi have been found in this chamber and they may take up the larger part of the cavity While the basic feature of this disease in both ventricles is the fibrosis, and this is usually located at the apex and on the posterior wall, other associated lesions may occur and the fibrosis may not be extensive It may be confined to the apex, to a region of the wall behind a papillary muscle or chorda, or to the region behind the posterior cusps without involving the apex. The muscle, chorda, or cusp may be fused to small areas of such fibrosis But where fibrosis occurs, it is at the apex or in the ventricular inflow tract and does not involve the outflow tracts below the semilunar valves.

The commonest associated lesion is superimposed *mural thrombosis*, which may vary from a brown-red or yellow-green discoloration of the usually pearly-white, glistening fibrous tissue to a massive intraventricular or atrial thrombus filling up most of the chamber. The largest thrombi are seen in the left ventricle. Occasionally, in either ventricle, a white spherical ball of fibrous tissue may be found at the apex which, on section, shows a dark central portion consisting of an old thrombus completely surrounded by fibrous tissue The more extensive the endocardial fibrosis, the greater the likelihood that there will be an overlying thrombus. A superimposed terminal *bacterial endocarditis* is sometimes seen *Calcification* of fibrous tissue is often seen varying from a few calcific specks to a large sheet of calcified endocardial tissue. This calcification is almost invariably seen in the superficial areas of the fibrous tissue, i.e., in the part nearest to the cavity. It is rarely found in the atria where large thrombi are not uncommon, particularly in the appendages

The fibrous tissue, particularly in the ventricles, may present a layered appearance with the denser white areas more superficially situated, while the deeper layers are darker in color and have strands of fibrous tissue extending from them deeply into the myocardium The fibrous tissue layer is often partly separated from the myocardium by a thin layer of engorged dilated blood vessels, and such dilated lagoons of blood may also be seen in the strands of fibrous tissue penetrating into the myocardium. The heart muscle beyond

tria, North America, and South Africa. Usually, in these instances, the hearts are enlarged and often very hypertrophied, in some, only single or multiple mural thrombi have been found, often giving rise to emboli, in others, there has been such extensive endocardial fibrosis that the term "constrictive endocarditis" has been used. Lesions similar to those termed "obliteration of the right ventricle" have been described. In those where there is marked endocardial fibrosis, the lesions are similar to those seen in endomyocardial fibrosis, though the extreme valvular conditions seen in the latter disease have rarely been reported, this may be because most reports deal with isolated cases or small groups of cases. If they are in fact identical, the geographical distribution of endomyocardial fibrosis is far wider than the African continent

At the same time there remains the problem that, outside tropical Africa, heart failure with mural thrombosis and resulting embolization is much more frequently reported than is endocardial fibrosis, whereas in tropical Africa the opposite obtains In areas where there is much coronary artery disease, endocardial fibrosis might be attributed to this rather than to some other form of heart disease But this is not true of South Africa where, in Africans, coronary artery disease is rare, heart failure with mural thrombosis and embolization is common, but endocardial fibrosis and valve involvement are rare In Uganda this is not so, and advanced fibrosis with valve involvement, without past or present embolization, is a common finding. If the lesions, thrombus-fibrosis, have a sequential relationship this is difficult to understand Where a late fibrotic state is common, one might expect to see many cases exhibiting mural thrombosis only or with partial fibrosis

Yet it is difficult to believe that the lesions of endomyocardial fibrosis could have arisen by any mechanism other than by the organization of mural thrombi, and the histological evidence does suggest that this has been the mechanism There is no evidence of any marked loss of myocardial tissue. However, providing that the formation of mural thrombi is an early lesion in endomyocardial fibrosis, then it must be either minimal or else it is speedily organized or covered by endothelium, for embolic lesions are rarely seen. If small in extent, the clot is presumably organized to produce the small fibrous plaques seen in some patients who have died without showing evidence of heart disease. If extensive, such thrombi must interfere with the endocardial-myocardial circulation, and this may in turn accentuate cardiac damage until the cardiac action is affected. Fresh thrombi may be deposited upon the old organized thrombi in the terminal stages of the disease and, because of the feebleness of the heart's action, may not be dislodged.

If this is the true pathogenesis of endomyocardial fibrosis, the initial cause of the cardiac damage and of the formation of mural thrombi remains quite obscure So far, no specific etiological evidence has been produced. It does not appear that any similar condition has been described in animals either spontaneously or under experimental conditions. An "aura" of malnutrition hangs over many cases of obscure heart disease in Africa and in other continents. But some patients have been well nourished while others have been recorded as visiting the tropics, which raises suspicion of an infective factor On the other hand, others have not been in the tropics Thus, the origin of endomyocardial fibrosis is obscure and will remain so for some time

On both clinical and pathological grounds, endomyocardial fibrosis appears to be a distinct entity, it is a major cause of heart disease in certain parts of Africa, it probably occurs in other continents, and the unraveling of its causes and pathogenesis may throw light on other forms of cardiac disease of obscure origin.

CLINICAL ASPECTS

The following account is based on clinical experience in East Africa, usually restricted to the late or terminal phases of the disorder The author does not know under what circumstances the earliest initial endocardial injury occurs, nor what clinical manifestations (if any) may accompany it and might enable a clinical diagnosis to be made at that early stage, if he were aware of them and knew exactly what to look for. Thus, the early his-

is a much more uncommon lesion. Thrombi in some of the cardiac chambers may reach such a size as to embarrass the heart, while the evidence of a terminal *bacterial endocarditis* may dominate the clinical picture. However, in the absence of such an endocarditis, it is remarkable how rarely there is either clinical or autopsy evidence of embolization from either side of the heart. This is in most striking contrast to the findings in other obscure forms of heart disease in which mural thrombosis is encountered.

RECOGNITION OF ENDOMYOCARDIAL FIBROSIS AND DISTINCTION FROM OTHER CONDITIONS

Two common conditions bear some resemblance to endomyocardial fibrosis. rheumatic heart disease and endocardial fibroelastosis. The late stages of rheumatic heart disease in Africans do not differ to any extent from the lesions seen in other races. Confusion with endomyocardial fibrosis can only arise where the lesions of this disease are confined to mural fibrosis adjacent to the atrioventricular valves. Points of distinction are (1) that the disease process in rheumatic heart disease, if the mural endocardium in the ventricle is affected at all, spreads from the valve, which is the most affected part, to the wall which is the least affected, (2) whereas in endomyocardial fibrosis the wall is most affected and the process spreads to the valve, the posterior cusp is most affected and the anterior cusps least affected, while the semilunar valves are not affected in endomyocardial fibrosis and, microscopically, rheumatic myocardial lesions are not found It is of course possible that both diseases are present in the same patient.

Distinction from endocardial fibroelastosis is usually easy and is confirmed by microscopy which reveals little or no elastosis in cases of endomyocardial fibrosis. Fibroelastosis is usually found in young children, though it does occur rarely in adults, the lesions are usually more clearly confined to the endocardium without any particular localization to the inflow tract, indeed involvement of the endocardium below the aortic valve is commonly seen The degree of endocardial thickening is rarely great and obliteration of the right ventricle does not seem to have been described. Other lesions of congenital nature are common and the semilunar valves are often involved In these respects fibroelastosis differs from endomyocardial fibrosis and when, in fibroelastosis, the atrioventricular valves are affected, they are not usually bound down to and engulfed in the mural endocardium as they are in endomyocardial fibrosis. Consideration of these points enables a distinction to be made between these conditions by gross examination, and this can be confirmed by histological examination. The lesions seen in ischemic heart disease, scleroderma, and diffuse lupus erythematosus clearly bear little resemblance to the lesions seen in endomyocardial fibrosis

ENDOMYOCARDIAL FIBROSIS AND OTHER OBSCURE FORMS OF CARDIAC DISEASE

As a specific entity, endomyocardial fibrosis has been described and characterized in Africans; in this disease the hearts may be atrophied or hypertrophied and embolic phenomena are distinctly rare. On the other hand, there are numerous reports from other continents and indeed from Africa as well, of patients with obscure forms of heart disease in which the hearts are usually hypertrophied, mural thrombosis is marked, and embolic phenomena are prominent and may dominate the clinical picture. In some of these cases, eosinophilia may be pronounced but endocardial fibrosis is often absent or minimal Such disorders have occurred in Europeans in West Africa, an area in which endomyocardial fibrosis is known to occur The clinical picture was one of obscure heart failure; there was a large heart with multiple embolic lesions and pronounced eosinophilia; the patients were well nourished, although they may have had a parasitic infestation capable of causing the eosinophilia. To this extent they differ from cases of Löffler's disease in which the eosinophilia is not due to a parasite but seems to be due to an allergic state, and widespread vascular disease due to allergy has been described in Löffler's disease. However such lesions have not been seen in endomyocardial fibrosis, in which no evidence of allergy has been found and eosinophilia is not common. Nor have allergic lesions or eosinophilia been marked in other cases of obscure heart disease with endocardial fibrosis or mural thrombi which have been recorded from France, Aus-

rior), an appearance accentuated where the aorta is small (Fig 16-27). In the right oblique view, a barium swallow will often outline an enlarged left atrium, though seldom to the extent seen in tight mitral stenosis, on the other hand, though the evidence of static left atrial enlargement is likely to be less than in stenosis, a *dynamic enlargement* with vigorous systolic expansion of the atrium in the oblique or posteroanterior views is sometimes striking This is important suggestive evidence of free organic regurgitation, though it is known that it is not pathognomonic and that it is sometimes absent in cases with typical mitral incompetence

Electrocardiographic evidence of atrial enlargement, namely, a disproportionately large P wave, or a lengthened P-R interval in the absence of mitral stenosis or pulmonary heart disease, are other suggestive findings

Thus the patient with endomyocardial mitral incompetence somewhat resembles the patient with rheumatic mitral disease in failure However, there is no opening snap, no diastolic or presystolic murmur, and no loud 1st sound, as in mitral stenosis, there is, on the contrary, a loud systolic murmur (and thrill), and a large left ventricle

Rheumatic mitral stenosis with severe incompetence, when the systolic murmur may have a harsh or squeaky quality, or with bacterial endocarditis, will be more difficult to distinguish When the diastolic murmur disappears, as it may do terminally in severe heart failure from mitral stenosis (Gorlin, 1954) or with the onset of atrial fibrillation, the distinction may be impossible clinically, though the history will usually be longer and fibrillation more likely in rheumatic disease

A *systolic murmur at the apex* is one of the most common of all physical signs, and is no evidence by itself of mitral incompetence, let alone of endomyocardial disease But when this is a loud murmur in a large, failing heart, there will usually be features of etiological significance· bacterial endocarditis, rheumatic or congenital disease, hypertension, severe anemia, thyrotoxicosis. When these can be excluded, and when there is the combination of a large left atrium and a large left ventricle, a large P wave, and a murmur of peculiar harshness and pitch, then endomyocardial mitral incompetence has to be considered, especially in a part of the world where endomyocardial disease is known to occur.



Fig. 16-27. Roentgenogram of patient with severe mitral incompetence due to endomyocardial fibrosis of left ventricle

TRICUSPID INSUFFICIENCY

Tricuspid incompetence as an isolated lesion with clear-cut physical signs is less common Endomyocardial disease of the right ventricle, extensive enough to involve the tricuspid, is likely to produce its characteristic obliterative features, thus obscuring the pure tricuspid signs Occasionally, however, cases of endomyocardial disease are seen which present tricuspid incompetence and the picture of right heart failure. Jugular vein engorgement and pulsation are present with prominent systolic pulsations, great hepatic enlargement, gross ascites, and edema. Expansile pulsation of the enlarged liver is to be expected but is not a constant finding. A systolic murmur may be heard at the lower end of the sternum

A large, globular heart shadow is seen on fluoroscopy without special enlargement of the left atrium or ventricle. Vigorous pulsation (systolic expansion) of the superior vena cava and right atrium may be observed but is not likely to be marked in the presence of extensive obliterative fibrosis of the right ventricle.

OBLITERATIVE FIBROSIS OF RIGHT VENTRICLE

Clinically severe right ventricular fibrosis resembles constrictive pericarditis more than anything else (Fienberg and Holzman, 1951). There is a greatly reduced diastolic filling of

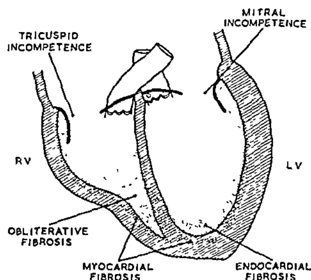


Fig. 16-26. Endomyocardial fibrosis. Distribution of lesions, valvular, endocardial, and myocardial, which may occur separately or in combination.

tory of the illness is not known. No association with previous cardiovascular, rheumatic, allergic, or pyrexial episodes has been observed, nor any constant association with previous infection, severe anemia, avitaminosis, or other nutritional deficiency. This is not unlike the situation of chronic mitral disease in the past, the condition was familiar to pathologists and clinicians but was not yet recognized to be the result of rheumatic fever. In its later stages, strikingly different clinical pictures are presented in rheumatic heart disease; pure mitral stenosis, isolated aortic incompetence, tricuspid stenosis, or the occurrence of two of them together may modify their distinctive clinical manifestations, as may the existence of a considerable degree of incompetence in a case of mitral stenosis In the same way, the clinical features of a particular case of endomyocardial fibrosis are determined by the site of the major endocardial lesion (Fig. 16-26) This may be confined to the left or right ventricle or may involve both, it may also grossly affect either mitral or tricuspid valve function, or both valves together, or neither, all of this resulting from an entirely similar pathology, the clinical signs depending upon its location in the heart or the site of its maximum severity.

One may encounter a number of sharply distinctive clinical patterns (Ball et al , 1954) in the late stages of endomyocardial fibrosis as well as some overlapping and much less distinctive patterns. These are: mitral insufficiency, tricuspid insufficiency, right ventricle obliterative fibrosis, combination of any of the above lesions, or heart failure without evidence of any of the above lesions

Bacterial endocarditis may be added to any of these. Also, but surprisingly seldom in the author's experience, single or repeated embolic episodes may occur with or without additional infection. Aortic or pulmonary signs are not encountered in endomyocardial fibrosis

The clinical lesions diagnosed in 24 cases in which endomyocardial fibrosis was confirmed at autopsy are given in Table 16-3

MITRAL INSUFFICIENCY

The first symptom is usually *shortness of breath,* sometimes with paroxysmal nocturnal dyspnea. But right-sided failure often supervenes quickly, so that edema and venous engorgement are usually present when the patient is first seen. The heart is enlarged and may suggest obvious left ventricle hypertrophy with a heaving apical impulse, or may be dilated and inert. There is *a loud systolic murmur* at the apex, often of a remarkably high pitch and with a harsh, dry, or squeaking quality. There may be a systolic thrill. There is no diastolic murmur.

Radiography may reveal no more than a diffuse enlargement of the heart, especially when pleural effusion obscures the picture. If the right heart is much enlarged, there may be close resemblance, in the posteroanterior view, to the squarish shadow commonly referred to as "mitralization" and associated with rheumatic mitral stenosis But when the left ventricle is much enlarged, as it often is in endomyocardial disease and especially in those cases with mitral incompetence, *this* will modify the squareness of the left border and give a more triangular shadow (posteroante-

TABLE 16-3 CLINICAL ANALYSIS OF 24 CASES OF ENDOMYOCARDIAL FIBROSIS

Clinical evidence		*No. of cases*
Mitral incompetence		7
Mitral and tricuspid incompetence		2
Tricuspid incompetence		1
Obliterative (right ventricle) fibrosis		2
Heart failure without any of the above		
Bilateral heart failure	9	12
Left heart failure	2	
Right heart failure	1	
Total		24

not always tally with the appearance or weight of the heart at autopsy. This anomaly can arise from great dilatation of one or both atria or of the pulmonary outflow tract which contribute to the size of the cardiac shadow out of proportion to what they add to the weight of the organ or to its size when they are emptied of blood after death. Again, recalling the rigid fibrotic or calcified plaques, of considerable extent in some hearts, one cannot be surprised if enlargement takes place in a somewhat bizarre fashion, the ability of a chamber to dilate must vary markedly from one part of its wall to another and the radiographic appearance predicted for a particular lesion may not occur On fluoroscopy, lack of detectable pulsations is common and can be very deceptive This appearance is more often to be explained by gross dilatation than by effusion Paracentesis may be needed in order to exclude tuberculous pericarditis. The detection of calcification, if constrictive pericarditis were excluded, would be a very suggestive finding. This has not so far been observed in the course of clinical radiography, but the appearance in a post-mortem roentgenogram of the isolated heart (Fig. 16-28) indicates what may be expected

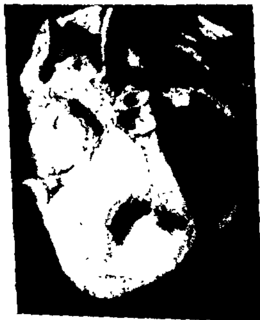


Fig. 16-28. Endocardial calcification in right ventricle radiographic appearance of the *isolated* autopsy specimen.

TABLE 16-4. INCIDENCE OF ABNORMAL ELECTROCARDIOGRAPHIC FINDINGS IN 24 CASES OF ENDOMYOCARDIAL FIBROSIS

ECG finding		*No of cases*
QRS less than 0 5 mv in limb leads		12
P exceeding 0.20 mv, or 0 11 sec		13
Atrial extrasystole		2
Atrial fibrillation		1
P-R exceeding 0 20 sec		6
Atrioventricular block		0
QRS exceeding 0.10 sec in any lead		1
Left bundle branch block	0	
Incomplete left branch block	3	4
Left ventricle hypertrophy	1	
Right bundle branch block	0	
Incomplete right branch block	2	5
Right ventricle hypertrophy	3	
Ventricular extrasystole		2
S-T deviation, without digitalis		0

Abnormal cardiograms are frequently present in the late stages of endomyocardial disease These may show evidence of atrial hypertrophy or strain, atrial fibrillation occasionally occurs. There may be right or left ventricular hypertrophy. Minor degrees of conduction disturbances, such as lengthened P-R interval or incomplete bundle branch block may occur. Flat and inverted T waves are common but the Q- and T-wave changes of infarction and necrosis are not seen in endomyocardial fibrosis; nor is significant S-T deviation a feature in the late stages of the disease which have been studied Low-voltage curves are common Cardiographic findings in 24 cases are summarized in Table 16-4. Clinical diagnosis and autopsy findings in the same patients are given in Tables 16-3 and 16-5 respectively.

As with the physical signs in this disease, there is no uniform or diagnostic cardiographic pattern This is due to the great variety in situation and extent of the endocardial and myocardial lesions and of their effects in producing hypertrophy or dilatation of particular chambers, also, because the muscle affected is confined to an extremely narrow zone, is separated from the electrode (in all leads except aVR) by a much thicker zone of undamaged myocardium, and is not (in the late stage of the disease) undergoing active injury or necrosis; in the last two respects, this is the opposite of acute pericarditis

The lack of any early history has been stressed. There is no consistent association with disease of other organs or systems In East

the right ventricle. Here again, jugular venous pressure, hepatic enlargement, and ascites are disproportionate to the symptoms. Tricuspid incompetence is absent or is overshadowed by the gross ventricular lesion; there is, therefore, no pulsation of the cervical veins or liver, and no tricuspid systolic murmur.

Roentgenology fails to supply characteristic data. There is no systolic expansion of the right atrium or superior vena cava. The right atrium and pulmonary outflow tract, however, may be severely dilated. Thus, a large shadow may serve to distinguish from constrictive pericarditis, but may be less easy to distinguish from earlier tuberculous pericarditis with effusion or with severe caseous and edematous thickening of the pericardium. Furthermore, endomyocardial disease may be accompanied by pericardial effusion. A classical feature of constrictive pericarditis, namely, calcification of the pericardium, is absent in endomyocardial disease. On the other hand, there is often considerable endocardial calcification; the possibility of this being mistaken for pericardial calcification on fluoroscopy or in the x-ray film should be kept in mind (Fig. 16-27).

Those patients with predominantly right ventricular endomyocardial disease may have signs out of proportion to their symptoms, and be relatively unembarrassed and have longer histories and survival than those with involvement of the left ventricle or both ventricles. Nonparoxysmal dyspnea, however, is sometimes present; this may be from several or from a combination of causes: pleural or pericardial effusion, or impeded diaphragmatic breathing due to ascites and liver enlargement.

COMBINED ENDOMYOCARDIAL LESIONS

Endomyocardial disease usually involves both ventricles with or without one or both atrioventricular valves. Thus, patients presenting one of the distinctive clinical patterns described above are a minority. The variety of possible, and actual, combinations, and the intergrading of clinical patterns which they produce, is considerable and complicates clinical diagnosis.

One possible variety is represented by a moderate degree of mitral stenosis, occasionally complicating incompetence of this valve, very rarely to an extent sufficient to produce a diastolic murmur. Tricuspid and mitral insufficiency is a common combination. Obliterative fibrosis of the right ventricle may occur with tricuspid or mitral incompetence or both. The association of predominantly right or left ventricular failure with tricuspid or mitral involvement is not consistent.

It is not surprising that a cardiac disorder producing such a variety of anatomical deformities and functional disturbances (more often in combination than separately) should have escaped recognition as a clinical entity for such a long time and should often still defy diagnosis during life.

HEART FAILURE WITHOUT VALVULAR OR OBLITERATIVE LESIONS

The harmful effects of endomyocardial fibrosis are not confined to the valves. Extensive involvement of the wall of the ventricle is possible without affecting the AV valves and without gross obliterative effect, particularly in the left ventricle. Such cases present heart failure without special features. The heart is enlarged; there may be a soft systolic murmur at the apex or no murmur. It may be clear from the history that exertional dyspnea has preceded other symptoms, suggesting initial left ventricular failure; this, however, fails to give a clue to the pathologic changes, except that the absence of hypertension and of coronary or aortic disease may give a lead. In other cases, heart failure develops without indicating predominant involvement of one side more than the other.

DIAGNOSTIC CONSIDERATIONS

All too often, diagnosis can only follow a careful exclusion of the better-known possible causes for the signs and symptoms, considered in relation to the local incidence of heart diseases where the patient lives or has traveled. A diagnosis of endomyocardial fibrosis will not be made lightly in a country where many autopsies are performed and yet endomyocardial fibrosis is never seen. Unfortunately, neither radiography nor electrocardiography are of more than limited value, for reasons which will be discussed below.

Radiographic and Fluoroscopic Findings. These findings, in cases of pure mitral and tricuspid incompetence, may be characteristic. In general, the radiographic appearance does

not always tally with the appearance or weight of the heart at autopsy. This anomaly can arise from great dilatation of one or both atria or of the pulmonary outflow tract which contribute to the size of the cardiac shadow out of proportion to what they add to the weight of the organ or to its size when they are emptied of blood after death Again, recalling the rigid fibrotic or calcified plaques, of considerable extent in some hearts, one cannot be surprised if enlargement takes place in a somewhat bizarre fashion, the ability of a chamber to dilate must vary markedly from one part of its wall to another and the radiographic appearance predicted for a particular lesion may not occur. On fluoroscopy, lack of detectable pulsations is common and can be very deceptive. This appearance is more often to be explained by gross dilatation than by effusion Paracentesis may be needed in order to exclude tuberculous pericarditis The detection of calcification, if constrictive pericarditis were excluded, would be a very suggestive finding This has not so far been observed in the course of clinical radiography, but the appearance in a post-mortem roentgenogram of the isolated heart (Fig 16-28) indicates what may be expected



Fig 16-28. Endocardial calcification in right ventricle, radiographic appearance of the isolated autopsy specimen.

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[illegible]		1
[illegible]		6
[illegible]		0
[illegible]		1
Incomplete left branch block	3	4
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Right bundle branch block	0	5
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Radiographic and Fluoroscopic Findings. These findings, in cases of pure mitral and tricuspid incompetence, may be characteristic In general, the radiographic appearance does

may extend into the myocardium *Marked left ventricular hypertrophy* is almost always present and *right ventricular hypertrophy* is frequently seen Two types of subendocardial fibroelastosis may be recognized on the basis of the appearance of the left ventricle. the *dilated type* and the *contracted type*, the former is more common than the latter (Edwards). It is presumed that the thickened endocardium interferes with and limits the expansion and contraction of the ventricle from the inside in much the same way as does the scar tissue deposited around the heart in constrictive pericarditis (Thomas). Thus, this condition is sometimes called "constrictive endocardial sclerosis." Angiocardiographic findings may show small change in systolic and diastolic volume of the left ventricle (Gasul; Linde) It is important to recognize that fibroelastosis may be secondary to an obstructive lesion such as aortic or mitral stenosis, or secondary to anomalous origin of the left coronary artery from the pulmonary artery Such instances are not considered in the present discussion

A brief discussion of the conditions encountered in constrictive pericarditis is appropriate

HEMODYNAMICS OF CHRONIC CONSTRICTIVE PERICARDITIS

Hemodynamic studies of chronic constrictive pericarditis and related conditions have helped greatly in understanding the hemodynamic changes associated with subendocardial fibroelastosis The classical description of the pathophysiology of chronic constrictive pericarditis was given by Chevers over 100 years ago. He stated "The principal cause of dangerous *symptoms* appears to arise from the occurrence of gradual contraction in the layer of adhesive matter which has been deposited around the heart, compressing its muscular tissue, and embarrassing its systolic and diastolic movements, but more particularly the *latter*" Impairment of diastolic filling of the ventricles is characteristic of constrictive pericarditis but may occur in other conditions These include diffuse *myocardial fibrosis*, *endocardial fibrosis*, *primary amyloidosis of the heart*, and *pericardial effusion* (Clark). Cardiac catheterization in these conditions and in chronic constrictive pericarditis may reveal characteristic alterations in the pressures and flows Similar, but usually less marked changes, have also been observed in *congestive heart failure*. Chronic constrictive pericarditis usually involves the left and right ventricles to a similar degree. Most of the information which follows relating to this condition has been obtained by right heart catheterization However, left ventricular pulse pressures obtained at the time of surgery have been reported (Hansen). When constrictive pericarditis predominantly involves the left ventricle, right heart catheterization data show evidence of pulmonary hypertension, secondary to the elevated left ventricular diastolic pressure (White, 1948). Constriction of the atria is rarely, if ever, of primary importance in constrictive *pericarditis (Isaacs)*.

A serious consequence of impairment of diastolic filling is a *reduced stroke volume* and a *reduced cardiac output* An increase in the cardiac output on exercise is accomplished under these conditions *entirely by increasing* the heart rate The pressure pulse records usually show a marked elevation of the mean right atrial and right ventricular diastolic pres-

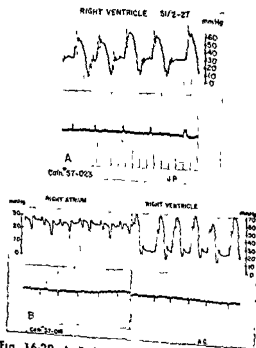


Fig. 16-29 A Right ventricular pressure-pulse tracing of a patient with a constricting band over the anterior part of the heart illustrating early-diastolic dip and plateau. B. Right atrial and right ventricular pressure-pulse tracing of a patient with constrictive pericarditis, illustrating the two dips in the atrial tracing, the more prominent dip occurring in early diastole.

TABLE 16-5 SITES AFFECTED, AND SITES OF MOST SEVERE LESION, IN 24 CASES OF ENDOMYOCARDIAL FIBROSIS AT AUTOPSY

Sites of endocardial fibrosis	No. of cases	
	Chamber or valve affected in any degree	Chamber or valve severely affected
Right ventricle, without obliterative fibrosis	11 } 18	4 } 11
Right ventricle, with obliterative fibrosis, apex	7	7
Tricuspid valve structures	5	
Right atrium..	7	
Left ventricle	22	13
Mitral valve structures	12	
Left atrium	4	
Total		24

African patients with endomyocardial fibrosis, considerable *splenomegaly* has been noted in some, and is absent in others, the same can be said of *eosinophilia*. *Embolism* from mural thrombi, pulmonary or systemic, may occur. It has been observed in East African patients with endomyocardial fibrosis less often then in similar cases (Gray, 1951) reported from other parts of the world.

Differential diagnosis requires consideration of rheumatic heart disease, tuberculous pericarditis, bacterial endocarditis, and congenital heart disease Severe anemia and liver cirrhosis (both of which may occur as complications) may also simulate endomyocardial fibrosis in certain features, as may nutritional heart disease (Gillanders, 1951), and the heart in chronic alcoholism and beriberi The clinical differentiation of endomyocardial fibrosis from the ill-defined group of myocardial disorders of unknown origin (isolated myocarditis and others) must often remain exceedingly difficult or impossible.

TREATMENT AND PROGNOSIS

Without knowledge of cause or pathogenesis and without a basis for early diagnosis, a rational therapy to arrest or reverse the condition before fibrosis has advanced to a damaging extent is not available. That the lesion can be self-arresting, and that even extensive fibrosis can be present without cardiovascular symptoms if valves and myocardium are not severely affected, is clear from autopsy findings of endomyocardial fibrosis unrelated to the cause of death If the author cannot yet say that this is a preventable disorder, he can at least infer that, if it could be detected and arrested at an early stage, satisfactory cardiac function could be preserved. A rationale for an early etiological treatment which would be effective in arresting the thrombofibrotic process is therefore much to be desired.

The late endocardial and valve lesions are *not* amenable to surgery. At this stage, the response of heart failure to *digitalis* and *mercurial diuretics* varies from patient to patient, some are able to resume sedentary ambulant activity for a few months, others remain bedridden with little or no improvement. Prognosis, once heart failure is established, is extremely poor. The majority do not survive beyond 1 or 2 years. The longest duration of symptoms has been recorded in patients with pure or predominant right ventricular lesions with or without tricuspid incompetence, two patients lived for 4 years and one for 8 years It is probable that survival is longest in cases of this kind, in whom both the pulmonary circulation and the left ventricle are protected from extremes of load

CARDIAC CATHETERIZATION IN SUBENDOCARDIAL FIBROELASTOSIS AND CONSTRICTIVE DISEASES [1]

SUBENDOCARDIAL FIBROELASTOSIS

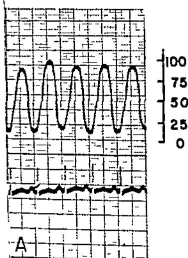
This is a condition of unknown cause characterized by a diffuse thickening of the endocardium, associated with cardiac hypertrophy, and most frequently involving the left ventricle and left atrium. The right heart chambers are rarely involved The endocardium is diffusely thickened, smooth, and porcelain-white The valves are also affected at times. The subendocardial thickening is due to a marked proliferation of the collagen and elastic tissue which

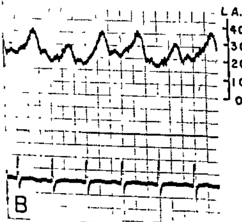
[1] This work was done in collaboration with the late Dr. R. F. Dillon.

diastole Some observers have emphasized that the ratio of the end-diastolic to the systolic pressure in the right ventricle does not exceed 1:3, except in chronic constrictive pericarditis (Yu). However, exceptions occur. The left atrial and left ventricular pressure pulses also show an early-diastolic dip and plateau in constrictive pericarditis. A marked elevation of the pulmonary wedge pressure is usually present, indicating left ventricular involvement In fact, the mean right atrial and pulmonary wedge pressures in chronic constrictive pericarditis are usually approximately equal because the alteration in ventricular distensibility involves both ventricles to a similar degree. The pulmonary arterial pressure usually shows a small pulse pressure because there is a marked increase in the diastolic and very little rise in the systolic pressure (Burwell). In response to exercise, a further rise in the right atrial, right ventricular, pulmonary artery, and pulmonary wedge pressures is observed

HEMODYNAMICS OF SUBENDOCARDIAL FIBROELASTOSIS

This condition is rare. Although it may occur in adults, most of the cases occur in the pediatric age group The published data of right heart catheterization in patients with subendocardial fibroelastosis report normal or slightly increased pulmonary artery and pulmonary wedge pressures (Adams). Of 26 patients with subendocardial fibroelastosis studied by the authors, six, ranging in age from 6 months to 10 years, have been studied by right heart catheterization. In four of these patients, left heart catheterization was also performed The findings of left heart catheterization, to the best of the authors' knowledge, have not been reported previously by other authors. In four patients, the diagnosis was confirmed at autopsy The right heart cathe-





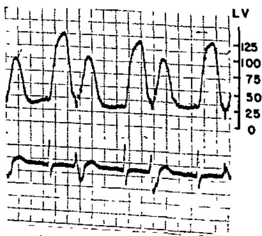


Fig 16-30 A Left ventricular pressure-pulse tracing showing high left ventricular diastolic pressure, there is no evidence of an early-diastolic dip and plateau. B. Record of left atrial and left ventricular pressure pulses Bigeminy is present during recording of left ventricular pressure pulses. There is no evidence of an early-diastolic dip and plateau

TABLE 16-6. RIGHT HEART CATHETERIZATION DATA ON SIX PATIENTS WITH SUBENDOCARDIAL FIBROELASTOSIS

Case	Age	Sex	Pressure, mm Hg				Pulm. resistance		O_2 sat %	CI
			R.A	R.V.	P.A.	P.C	Total	Arteriolar		
1	6 mo	M	3	96/2	96/44	26	7,262	3,890	95.8	1.86
2	10 mo	M	4	49/6	50/28		2,780	.	96.5	3.39
3	18 mo	M	6	49/2	50/23	17	1,460	770	93.7	4.17
4	3½ yr	F	5	34/5	38/17	10	1,100	600	92.1	3.31
5	6 yr	F	5	89/6	89/48	19	3,205	2,367	93.8	2.1
6	10 yr	M	5	52/5	52/24	20	1,540	708	99.2	2.37

R A = right atrium mean blood pressure
R V = right ventricle
P A. = pulmonary artery
P C. = pulmonary capillary or wedge

Pulmonary resistance is in dynes/sec/cm^{-5}
O_2 sat % = peripheral arterial oxygen saturation
C I. = cardiac index

sures and a prominent, *early-diastolic dip* in the atrium and ventricle (Bloomfield) The early-diastolic dip is followed by a plateau These phenomena are best seen in the ventricular pressure-pulse tracings (Fig 16-29A). There are two well-marked negative waves (dips) in the right atrial pressure tracing during the cardiac cycle, one in early diastole, the other during ventricular systole (Fig. 16-29B).

In the normal heart, the volume changes associated with filling of the ventricles result in only slight pressure changes. When ventricular distensibility is impaired, marked changes in pressure occur. Hence the catheterization data show elevation of the right ventricular diastolic and the mean right atrial pressures. Because the maximal diastolic volume of the ventricle is fixed, ventricular filling is rapidly completed, and the pressure tracing shows a sharp rise after the early diastolic dip and a sustained high pressure, referred to as a *diastolic plateau*, during the remainder of

TABLE 16-7 LEFT HEART CATHETERIZATION DATA ON FOUR PATIENTS WITH SUBENDOCARDIAL FIBROELASTOSIS

Case	Age	Sex	Pressures, mm Hg			
			Left atrium *	Left ventricle		
				Early diastole	Late diastole	Systolic
3	2½ yr	M	26	23	23	113 † 88
4	3½ yr	F	12		13	92
5 ‡	6 yr	F	22			
6	10 yr	M	28	24	29	104

* Left atrium mean pressures
† Pressures recorded during ventricular bigeminy
‡ Left ventricle *not* entered in this patient
Case No 3: First catheterization at age 18 months (see Table 16-6); second catheterization at age 2½ years

also compatible with myocardial impairment or failure may be encountered in fibroelastosis associated with slight left ventricular dilatation or in the contracted rather than the dilated type of fibroelastosis. In the latter, the physiologic findings appear to be simply those of left ventricular failure with an elevated left ventricular diastolic pressure and no characteristic changes in the pressure pulse contours. The right heart catheterization data usually demonstrate mild to moderate pulmonary hypertension. The pulmonary wedge pressures are usually elevated. These findings are secondary to the changes involving the left side of the heart. Further study of this subject is certainly indicated.

terization data showed *variable degrees of pulmonary hypertension,* which was mild to moderate in four. The pulmonary artery systolic pressures ranged from 34 to 56 mm Hg. In two patients, however, the pressures were more than 80 mm Hg. One of the latter patients showed at autopsy some degree of mitral stenosis besides fibroelastosis of the left ventricle; the other patient had no evidence of mitral stenosis at autopsy. The pulmonary wedge pressures were definitely elevated in four patients, normal in one, and not obtained in another. The calculated total pulmonary resistances were elevated in all patients and markedly increased in the two who had pulmonary pressures greater than 80 mm Hg. The pulmonary arteriolar resistances were also *markedly increased* The peripheral arterial oxygen saturation was normal, except in one patient in whom it was very slightly diminished. The calculated cardiac index was within the range of normal in three but diminished in the other three patients (Table 16-6).

Because of the presumption that subendocardial fibroelastosis behaves like constrictive pericarditis when it involves the left ventricle, it is of interest to determine whether the left ventricular pressure-pulse changes resemble those of constrictive pericarditis This problem may be solved by combined right and left heart catheterization Indeed, without left heart catheterization data, it is not possible to be sure whether pulmonary hypertension and elevation of the pulmonary wedge pressures reflect a mitral valve lesion, involvement of the left ventricle, or a combination of these lesions.

The mean left atrial pressures were markedly elevated in three patients, and slightly elevated in one (Table 16-7). In two of these patients, the left ventricular diastolic pressures corresponded with the left atrial pressures at similar times in the cardiac cycle. In one patient, besides an elevated left ventricular diastolic pressure, there was an increase in the "left atrial V" wave suggestive of slight mitral regurgitation,[2] these findings are consistent with the valvular changes seen in this condition. In one patient in whom it was not possible to enter the left ventricle, but only the left atrium, no evidence *of mitral stenosis was found* at autopsy. In all three patients, the left ventricular diastolic pressures were elevated to levels consistent with left ventricular failure The left ventricular pulse-pressure tracing revealed *no evidence* of an early-diastolic dip and plateau in two patients (Fig 16-30). In one patient, the tracing showed an early-diastolic dip followed by a sharp rise in pressure, the latter being due in part to atrial contraction which gives the impression of a short diastolic plateau (Fig 16-31) It is of interest to note that this patient (now 10 years old) has never been in heart failure, showed only slight to moderate cardiac enlargement on radiography, and had moderate pulmonary hypertension and a left ventricular end diastolic pressure of 29 mm Hg Four years previously, a negative surgical exploration for suspected mitral stenosis had been performed Excision of the left atrial appendage revealed marked thickening due to fibroelastosis. It is presumed that the same condition is present in the left ventricle The two patients whose left ventricular pressure tracings revealed no evidences of an early-diastolic dip and plateau had been in heart failure previously, showed evidence of cardiac enlargement, and their heart rates were faster than that in the previous patient.

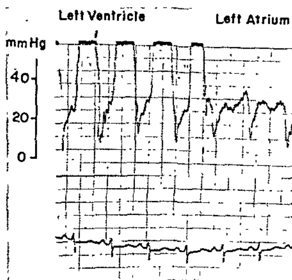


Fig. 16-31. Left ventricular and left atrial pressure pulse obtained by pull-back from left ventricle, illustrating early-diastolic dip followed by sharp rise in pressure.

CONCLUSIONS

These facts suggest that hemodynamic findings compatible with a constrictive lesion but

[2] The so-called left atrial V wave is actually a late-systolic wave of regurgitation For details, see Part 4, Chap 12 and Part 7, Chap. 14. *Editor.*

ble, at least in their superficial portions The more frequent multiverrucous type appears as a band of yellowish-tan *verrucae* or vegetations at the line of closure of a moderately thickened valve. Involvement of the commissures and corpora arantii of the aortic valve is not infrequent, but the mural endocardium and valve pockets are characteristically spared. Although all valves may be affected, the mitral and aortic, either singularly or together, represent the most frequent sites of degenerative verrucal endocardiosis.

Microscopically, affected valves reveal focal or diffuse swelling and degeneration of valvular collagen The latter assumes a pronounced eosinophilia in sections stained with hematoxylin and eosin Remnants of collagen may be identified in such areas by appropriate staining techniques In addition, degenerated foci are argyrophilic, markedly resistant to tryptic digestion, and may appear orange when stained by the phosphotungstic acid–hematoxylin method (Allen and Sirota, Fisher and Baird) The tinctorial features are similar to those of fibrinoid rather than fibrin or unaltered collagen. Protrusion of this material on to the surface of the valve may occur and constitute the entire vegetation. More frequently, fibrin thrombi appear superimposed upon such an altered endocardial surface (Fig. 16-33) Similar foci of altered valvular collagen may be observed within the valve without apparent herniation. There is a notable paucity of inflammatory cells within the valve, although small collections of neutrophils, lipid-laden macrophages, and an occasional *Anitschkow myocyte* may be observed, particularly in superficial areas Bacterial masses are not encountered and culture of the vegetations is negative It is conceivable, however, that this condition may be encountered since bacterial growth may occasionally be obtained from apparently normal valves (Epstein and Kugel). It has been suggested that the so-called *excrescences of Lambl* may represent healed forms of degenerative verrucal endocardiosis (Allen and Sirota).

The absence of significant inflammatory reaction or destruction of the valve in degenerative verrucal endocardiosis readily allows for its differentiation from acute and subacute bacterial endocarditis. The former feature, as well as lack of Aschoff bodies, help distinguish it from rheumatic valvulitis Although morphologically the lesions of atypical verrucous endocarditis may appear identical with those of degenerative verrucal endocardiosis, the location of the former and its association with other visceral manifestations of lupus erythematosus allow for their differentiation.

The clinical significance of degenerative verrucal endocardiosis has been reemphasized by



Fig. 16-33. Section of aortic valve with verruca comprised of fibrin and fibrinoid Small foci of fibrinoid degeneration are also apparent within valve substance (1). Inflammatory reaction is characteristically absent.

I

Degenerative verrucal endocardiosis

EDWIN R. FISHER

Degenerative verrucal endocardiosis (nonbacterial thrombotic endocarditis) is a form of valvular heart disease with macroscopic and morphologic features which are distinct from those of the bacterial, rheumatic, or syphilitic types. The term is synonymous with "nonbacterial thrombotic indeterminate endocarditis" as used by Libman and Gross and Friedberg. Other designations, such as "terminal" or "marantic" endocarditis or *endocarditis simplex* or *minima*, appear unsatisfactory since they imply that these lesions are of little clinical significance or represent a terminal event during the course of a fatal illness. Indeed, they may be directly responsible for death (Fisher and Baird; MacDonald and Robbins), or act as a nidus for bacterial endocarditis (Allen and Sirota). The term "degenerative verrucal endocardiosis" (Allen and Sirota) aptly indicates the morphogenesis and noninflammatory nature of the lesions.

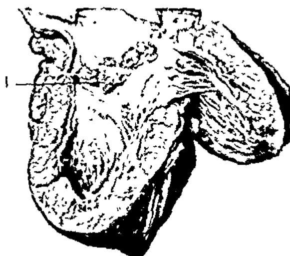


Fig. 16-32. Large multiverrucous form of degenerative verrucal endocardiosis of aortic valve (I) of heart from patient with mucinous carcinoma of lung

Although degenerative verrucal endocardiosis may be noted in a variety of diseases, approximately one-third of the recorded cases have been associated with *malignant neoplasms* and, in a similar number, *congestive cardiac failure* was apparent. It is of interest that arteriolar lesions with similar morphologic and tinctorial features may be observed in some patients with degenerative verrucal endocardiosis and carcinoma (Fisher and Baird) or thrombotic thrombocytopenic purpura (Friedberg and Gross; Singer et al.). The occurrence of this form of valvular disease in cases with inactive or chronic rheumatic heart disease has been emphasized (Gross and Friedberg). However, MacDonald and Robbins found the latter in only 18 per cent of 78 examples of degenerative verrucal endocardiosis. On the other hand, arteriosclerotic heart disease was encountered in more than one-half of their cases. In 10 per cent of the cases, evidence of antecedent heart disease was absent. There [illegible] ...lection for [illegible] have [illegible] ...ugh been observed at all decades of life, ... the majority have been noted after the age of fifty.

Grossly, the lesions may be variable. They may be solitary (univerrucous) or multiple (multiverrucous), and their size may range from several millimeters to one or more centimeters (Fig. 16-32). Small lesions are rather *firmly* adherent to the valves, whereas the larger, more globose types are somewhat fra-

14

Left atrial myxoma and ball-valve thrombus

WILLIAM LIKOFF

Primary tumors of the heart are uncommon. The most prevalent are *endocardial myxomas* which occur mainly within the atria. A controversy exists as to whether these structures are true neoplasms or *thrombi* which have undergone myxomatous degeneration. Because this uncertainty cannot be resolved, left atrial myxomas and ball-valve thrombi are considered as a generic topic in the present discussion.

Recent diagnostic refinements have reduced the difficulty of recognizing these lesions. Precise studies, such as angiocardiography, have made it possible to correlate their presence with the signs and symptoms which they initiate. Of equal importance, these actual or pseudotumors have been removed successfully under hypothermia or with the aid of the cardiopulmonary bypass. This promise of proper recognition and effective treatment accounts for the intense interest currently being expressed on a subject which heretofore had been considered singularly rare and unimportant.

PATHOLOGICAL CONSIDERATIONS

Approximately 80 per cent of intraatrial tumors occur on the left side. They arise in the region of the mural endocardium, where the preferred sites of origin include the area of the foramen ovale, the pulmonary veins, and the auricular appendage, or from the heart valves themselves, most notably the mitral.

In the early medical literature these lesions generally were considered neoplastic (Thorel). More critical evaluation of the illustrations cited indicated that they actually represented thrombi in various stages of organization (Husten). However, many authors continue to favor the interpretation that these atrial tumors are cellular in origin. Support for this position is derived from the following observations: (1) They are not found in the ventricles, where thrombus formation is so common. (2) They frequently occur without concomitant thrombus formation in the adjacent appendage. (3) There rarely is evidence of stratification, which would be expected in thrombi. (4) On microscopic examination, stellate cells, lymphocytes, and plasma cells, all characteristic of a neoplasm, are observed.

Theoretically, there should be additional proof that these structures arise in a definite location and have a uniform appearance. However, those reported in the literature varied considerably in size, contour, and consistency. They have been thick and irregular or villous and smooth, they have been firm or gelatinous; they have been attached to the endocardium by a long, narrow stalk or by a broad base.

The microscopic findings also have been inconsistent (Fig. 16-34). The amorphous material forming the ground substance of the tumor has stained like mucin or has not. A great variety of cells has been seen including the stellate type, typical of myxomatous tissue, inflammatory elements, such as lymphocytes and plasma cells, large multinucleated structures; and

MacDonald and Robbins. Emboli with infarction were noted in 14 per cent of their cases, and in many of these such events dominated the clinical picture. The tinctorial features of the emboli are frequently identical with those of the valvular lesion, containing both fibrinoid and fibrin (Fisher and Baird). The role of degenerative verrucal endocardiosis in the pathogenesis of some cases of bacterial endocarditis has been indicated by Allen and Sirota.

The pathogenesis of degenerative verrucal endocardiosis has not been elucidated The possibility that such lesions may represent a manifestation of hypersensitivity, although attractive and not implausible, requires more convincing proof Further studies are necessary.

recurrent the symptoms are evanescent, identical with those usually encountered in rheumatic mitral stenosis, and out of proportion to the degree of demonstrable heart disease The diagnosis of this type of tumor may be further suggested by a negative past history for rheumatic fever However, approximately one-half of the patients with unmistakable rheumatic endocarditis have no knowledge of previous activity.

When the myxoma or ball-valve thrombus causes a sudden complete obstruction to ventricular filling, a curious type of circulatory failure develops, accompanied by a shock-like syndrome.

Occasionally, the mitral valve or the pulmonary vein openings are partially blocked by a myxoma which maintains a fixed position within the left atrium (Likoff et al) The clinical manifestations of this type of lesion cannot be differentiated from ordinary rheumatic *mitral stenosis*

Transient Mitral Valve Obstruction. A number of cases have been collected and reported in which polypoid myxomas or thrombi of the left atrium have brought about an intermittent occlusion of the mitral orifice This transient obstruction to blood flow produces the hemodynamic and clinical abnormalities of mitral stenosis. However, it has been a common experience that *these symptoms and signs are markedly altered by changes in body position, which influence the relation of the myxoma to the mitral valve opening.*

With the recurrent obstruction, there is an exacerbation of the ordinary symptoms of functional mitral stenosis including dyspnea. *Extreme respiratory embarrassment including pulmonary edema is more likely to develop in response to a particular position rather than to exercise.* This also characterizes such complaints as precordial discomfort and the sensation of a rapid or irregular cardiac action Certain uncommon manifestations have been encountered, especially *cyanosis*, *vertigo*, and *syncope*. On occasion, *convulsions accompany* the loss of consciousness

Rapidly developing and persistent heart failure also has been attributed to intraatrial myxomas which temporarily block the mitral valve or pulmonary vein openings In some instances, the sudden, unexpected, and *unexplained* development of heart failure has been quite remarkable However, as long as the tumor maintains a *changing* position in relation to the critically important intracardiac orifice, congestive *failure is not* intractable. If improvement occurs during ordinary therapeutic meas-

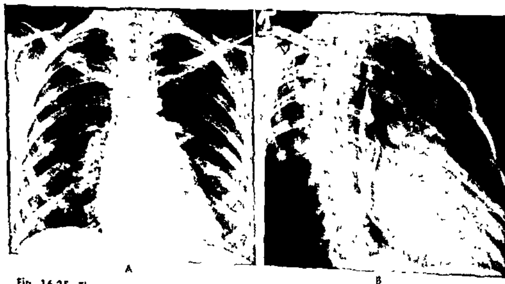


Fig 16-35. These roentgenographic pictures illustrate, (A) in the PA view, the fullness of the pulmonary segment giving rise to a "mitralized" left cardiac border, and (B) in the RAO, the posterior displacement of the barium-filled esophagus by the enlarged left atrium; seen in a patient with left atrial myxoma



Fig 16-34. The photomicrograph shows the structure of a myxoma removed from the left atrium. It clearly appears to be an edematous thrombus in the late stages of organization. The resemblance to edematous granulation tissue is striking.

erythrocytes Blood vessels have been observed, but even these vary very significantly in frequency and caliber. In many instances, they have appeared only as capillaries with endothelial walls through which the erythrocytes and the blood pigments hemosiderin and hematoidin have extravasated

Certain of these gross and microscopic findings have been listed as being most suggestive of a myxoma Thus, Gould, modifying the initial observations of Fabris, considers the diagnosis likely when the tumor arises in the area of the mitral valve or foramen ovale from a thin pedicled base, and when it is a thick, but transparent and soft, lesion with a continuous endocardial covering. On microscopic examination, stellate cells are distributed alone or in syncytial groups in a peculiar colorless stroma which stains like mucin.

In contrast, an organized thrombus is more likely to originate within the atrium as a regular, opaque, firm tumor with an endocardial covering only at the junction of implantation. The cells consist mainly of inflammatory elements and erythrocytes, which are stratified in several layers. Mucin is not present.

The ability to distinguish a myxoma from a thrombus frequently is compromised because certain features may be common to both lesions. For example, a myxoma may simulate a thrombus by containing a profusion of erythrocytes and hemosiderin microscopically, and by having fibrin on its free surface On the other hand, the center of a large organized thrombus may be replaced by fibrous tissue which can resemble diffusely distributed myxomatous material.

Acknowledging the complexity of the problem, Husten classified intraatrial tumors as either thrombi, myxomas, or structures which could not be accurately defined. Later, he questioned the existence of a true neoplasm and suggested that all of these lesions represented the end results of organized thrombi. This view deserves particular emphasis In all likelihood, it is reasonable and accurate. *All pedunculated structures arising from within the atria should be regarded as thrombi unless the evidence to the contrary is very compelling indeed* The major exceptions to this conservative view are the growths originating from the heart valves themselves, which are probably true tumors. These invariably are larger than most thrombi and are exceptionally well organized. The key sign that this or any other intracardiac myxoma represents an actual neoplasm which arises in rests of embryonic mucoid tissue is the demonstration of a localized proliferation of mucous tissue within the endocardium (Mahaim). However, the infrequency of this finding supports the concept that a myxoma is merely a thrombus which has undergone some degree of organization.

CLINICAL MANIFESTATIONS

Left atrial myxomas may be discovered during autopsies, even when previous histories and exacting physical, as well as laboratory, examinations have not suggested their presence It is not known how long these tumors do or can remain asymptomatic

On the other hand, myxomas can cause important clinical signs. These occur when they obstruct an orifice and impair the intracardiac flow of blood If the impediment to the flow of blood across the mitral valve is transient and

recurrent the symptoms are evanescent, identical with those usually encountered in rheumatic mitral stenosis, and out of proportion to the degree of demonstrable heart disease. The diagnosis of this type of tumor may be further suggested by a negative past history for rheumatic fever However, approximately one-half of the patients with unmistakable rheumatic endocarditis have no knowledge of previous activity.

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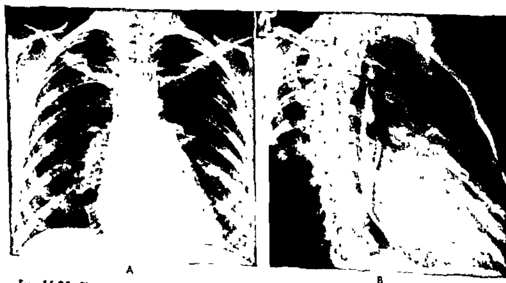


Fig. 16-35 These roentgenographic pictures illustrate, (A) in the PA view, the fullness of the pulmonary segment giving rise to a "mitralized" left cardiac border, and (B) in the RAO, the posterior displacement of the barium-filled esophagus by the enlarged left atrium, seen in a patient with left atrial myxoma.

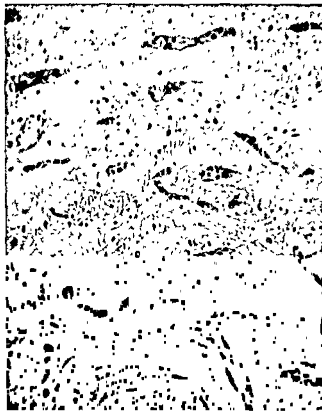


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The first successful operation was reported by Crafoord, who utilized hypothermia and an open technique This triumph now has been followed by others (Scannell et al, 1956).

It is evident that consistent results in the removal of left intraatrial myxomas are much more likely when the atrial wall is incised and the surgery is performed under direct vision. Otherwise, the risk of systemic arterial embolization from fragmentation of the tumor would be considerable. The use of the heart-lung pump to bypass the function of the left heart affords the means of an effective and reasonably safe approach to the problem.

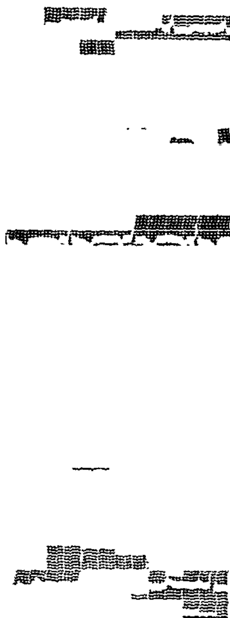


Fig. 16-36. The electrocardiogram shows bifid P waves in leads I and II and inversion of the T waves in leads II and III, seen in a patient with left atrial myxoma.

ures, the causative lesion still may remain obscure.

The *auscultatory findings* may be typical of mitral stenosis or may be bizarre and inconclusive. *In either instance,* the salient clinical point is the fact that the character, if not the actual presence of these events, may change with the position of the patient

The contour of the heart, as revealed by standard roentgenologic examination, may reveal straightening of the left border and prominence of the left pulmonary salient, accompanied by left atrial enlargement (Fig 16-35). These abnormalities, however, are modest when the obstruction to the mitral inlet is incomplete as well as transient. Very often this fact is the key to a proper diagnosis.

The *electrocardiogram* is not distinctive or helpful (Fig. 16-36). It may depict P-wave abnormalities or paroxysmal arrhythmias particularly atrial fibrillation or flutter. However, atrioventricular or intraventricular conduction defects and S-T segment or T-wave abnormalities, commonly reported in secondary tumors of the heart, are not usually encountered

Cardiac catheterization has indicated that, when an intraatrial myxoma causes a fixed degree of mitral valve obstruction, the pressures within the right ventricle, the main pulmonary artery, the left atrium, and the pulmonary capillary system become abnormally elevated (Mahaim). It is reasonable to suspect that a similar, but temporary, hemodynamic pattern is created when the obstruction is transient.

Angiocardiography is the most reliable method of making a definite diagnosis. The radiopaque material can be injected directly into the left atrium by utilizing the puncture technique employed in left heart catheterization. The myxoma then appears as a distinct filling defect (Fig. 16-35).

Sudden Complete Mitral Valve Obstruction. A large, pedunculated left atrial ball-valve myxoma or thrombus may completely occlude the opening of the mitral valve, critically impair left ventricular filling, and result in sudden death. This may occur without previous indications of an atrial tumor or it may succeed symptoms caused by a periodic impediment to ventricular filling.

Occasionally, when the complete obstruction develops gradually and inexorably, distinctive signs appear which suggest the diagnosis before the patient succumbs. The upper and lower extremities become cold and mottled *Localized areas of cyanosis and of actual necrosis appear at the tips of the fingers or toes.* Finally a state of profound shock develops and persists Death may not occur for several days, during which time consciousness may not be impaired

TREATMENT

Several unsuccessful attempts at surgical removal of left intraatrial tumors were reported in the first years after mitral commissurotomy became an established procedure.

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The first successful operation was reported by Crafoord, who utilized hypothermia and an open technique. This triumph now has been followed by others (Scannell et al, 1956).

It is evident that consistent results in the removal of left intraatrial myxomas are much more likely when the atrial wall is incised and the surgery is performed under direct vision. Otherwise, the risk of systemic arterial embolization from fragmentation of the tumor would be considerable. The use of the heart-lung pump to bypass the function of the left heart affords the means of an effective and reasonably safe approach to the problem.

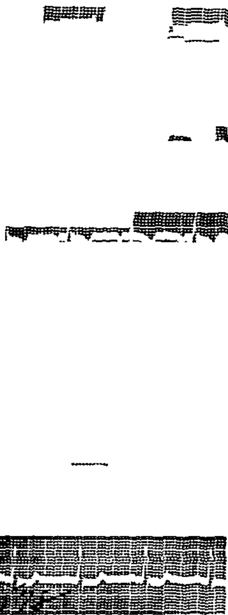


Fig. 16-36. The electrocardiogram shows bifid P waves in leads I and II and inversion of the T waves in leads II and III, seen in a patient with left atrial myxoma.

ures, the causative lesion still may remain obscure.

The *auscultatory findings* may be typical of mitral stenosis or may be bizarre and inconclusive. In either instance, the salient clinical point is the fact that the character, if not the actual presence of these events, may change with the position of the patient.

The *contour of the heart*, as revealed by standard roentgenologic examination, may reveal straightening of the left border and prominence of the left pulmonary salient, accompanied by left atrial enlargement (Fig. 16-35). These abnormalities, however, are modest when the obstruction to the mitral inlet is incomplete as well as transient. Very often this fact is the key to a proper diagnosis.

The *electrocardiogram* is not distinctive or helpful (Fig. 16-36). It may depict P-wave abnormalities or paroxysmal arrhythmias particularly atrial fibrillation or flutter. However, atrioventricular or intraventricular conduction defects and S-T segment or T-wave abnormalities, commonly reported in secondary tumors of the heart, are not usually encountered.

Cardiac catheterization has indicated that, when an intraatrial myxoma causes a fixed degree of mitral valve obstruction, the pressures within the right ventricle, the main pulmonary artery, the left atrium, and the pulmonary capillary system become abnormally elevated (Mahaim). It is reasonable to suspect that a similar, but temporary, hemodynamic pattern is created when the obstruction is transient

Angiocardiography is the most reliable method of making a definite diagnosis The radiopaque material can be injected directly into the left atrium by utilizing the puncture technique employed in left heart catheterization. The myxoma then appears as a distinct filling defect (Fig 16-35).

Sudden Complete Mitral Valve Obstruction. A large, pedunculated left atrial ball-valve myxoma or thrombus may completely occlude the opening of the mitral valve, critically impair left ventricular filling, and result in sudden death This may occur without previous indications of an atrial tumor or it may succeed symptoms caused by a periodic impediment to ventricular filling.

Occasionally, when the complete obstruction develops gradually and inexorably, distinctive signs appear which suggest the diagnosis before the patient succumbs. The upper and lower extremities become cold and mottled *Localized areas of cyanosis and of actual necrosis appear at the tips* of the fingers or toes Finally a state of profound *shock* develops and persists Death may not occur for several days, during which time consciousness may not be impaired

TREATMENT

Several unsuccessful attempts at surgical removal of left intraatrial tumors were reported in the first years after mitral commissurotomy became an established procedure. The tech-

PART 17

Borderline syndromes

PART 17

Borderline syndromes

1

Functional cardiovascular disturbances and the effects of stress

STEWART WOLF

All bodily disorders and diseases are functional and at the same time organic in the sense that they produce discomfort or disease in the patient by disturbing the function of one or more of the bodily organs, or organ systems Thus, congestive heart failure, irrespective of its etiologic basis, is a functional disturbance One of the major alterations in function is undue retention of salt and water All of the factors responsible for activating the pathogenic mechanisms are not understood They doubtless include weakness of the myocardium and ischemia of the kidney, but it is also apparent that, among other factors, impulses arising in the interpretive areas of the brain are capable of altering salt and water excretion They may thus enter the complex of congestive failure. Schottstaedt et al. have shown on one hand, a substantial diuresis of sodium and water and, on the other, a significant retention under differing stressful circumstances occurring in healthy subjects as well as those with impaired cardiac function Cathey et al have adduced evidence that stressful life situations may induce an elevation of serum cholesterol and lipoproteins of the S_f 12 to 20 range It is probable that most adaptive functions of the cardiovascular system are responsive to stimuli which owe their force to their special significance to the individual. Thus, like disorders of the gastrointestinal tract, cardiovascular disorders can probably be augmented or perhaps actually initiated by stressful life situations, as well as by antigens, microorganisms, or nutritional, climactic, and traumatic stresses

Much of the confusion concerning the role of life stress in disease derives from failure to distinguish between cause and mechanism. All *mechanisms* are perforce organic and at the same time functional since they involve the functions of units of the body's equipment *Causes*, on the other hand, are likely to derive from the outside, often from noxious stimuli in the environment The causes, which may be multiple, activate the pathogenic mechanisms and produce bodily disorders and disease. The ability of symbolic stresses to participate in the activation of disease mechanisms depends upon the fact that most bodily organs are connected with and responsive to impulses reaching them via autonomic and endocrine pathways from the highest integrative centers of the nervous system, the interpretive areas of the brain.

The behavior of the heart and its tributary vascular channels is largely subject to control by autonomic nerves, locally manufactured chemical vasomotor substances, and chemicals within the general circulation, as well as by mechanical stimuli Some of these alterations in vascular behavior result in changes of secretory function, as in the stomach, of excretory function, as in the kidney, and in changes of permeability of vessels They also may be manifest in the form of painful distention of vessels, as in migraine headache.

The blood vascular system is responsible for nourishing the cells of the body; its vessels

penetrate virtually every organ, provide intercommunications among certain organs, and serve to integrate their activities. Changes in structure and function of any of the bodily organs may be related fundamentally to changes in blood flow, in the contractile state, or in the permeability of vessels. Pressure changes in an organ related to adjustments in hemodynamics *may also be of importance, as in the glomeruli* or in the sinusoids of the liver or spleen. When, as in some diseases and bodily disorders, structural changes implicate the vessels, vasculitis and perivascular inflammation may occur or there may be degenerative changes in the vessels themselves.

Some forms of hydrocephalus, glaucoma, and dermatitis owe their mechanisms primarily to alterations in vascular function Blood vas*cular alterations are also of leading* importance in hepatic cirrhosis, pneumonia, and ulcerative colitis. In fact, inflammation itself is essentially a vasomotor adaptation The consequences of the vasomotor adjustments depend on the locality in which the changes occur. Thus, constriction of cranial arteries may induce neurological deficits of varying degree, and dilatation, headache. Vascular engorgement in the turbinates, on the other hand, *causes stuffy nose* and may trap pathogenic organisms in the nasal and paranasal spaces, leading to infection Elsewhere, the consequences of vasodilatation and vasoconstriction vary with the site In the skin, vasoconstriction conserves body heat In the efferent arteriole of the glomerulus, it increases the pressure of urine filtration. In the liver, pressure changes resulting from vasomotor effects are manifest in the arteriovenous shunts of hepatic c rrhosis *Even more widespread pressure changes in the* venous system occur as part of the syndrome of congestive failure, or in the arterial system as arterial hypertension

It is well established that changes in function of the heart or blood vessels accompany emotional reactions, such as anger or excitement In fact, wherever vasomotor adjustments have been studied, e g , in the eye, nose, skin, stomach, colon, and general circulation, it has been shown that they are subject to influence by meaningful life situations.

CARDIAC FUNCTION

Cardiac Output. The work of Wolf and Wolff (1946) and later of Hickman et al. established that variations in stroke volume and cardiac output correspond with changes in life situation and emotional state. Later Duncan et al. related them to some of the symptoms of neurocirculatory asthenia. The possible importance of such alterations in cardiac function to patients with already damaged hearts has not been assessed. It is noteworthy, however, *that the work of the heart may be increased* and its efficiency affected by circumstances which constitute figurative burdens.

Muscular effort is a familiar stimulus to cardiovascular function. On the basis of the predictability in degree and duration of changes evoked by measured amounts of exercise, various workers have devised tests of adequacy of cardiac function and of cardiac reserve.

Briefly, expected changes include temporary *tachycardia and increase in the heart's output* of blood with each beat (stroke volume), followed by return to resting levels at a rate depending upon the amount of exertion undertaken. In healthy subjects, changes in the pattern of the electrocardiogram do not ordinarily occur with exercise; when they do, they are thought to indicate a degree of cardiac insufficiency and a reduction of the reserve capacity of the heart.

Tests of exercise tolerance have been difficult to interpret because factors other than exercise are capable of inducing tachycardia, increase in stroke volume, and even T-wave changes in the electrocardiogram (Stevenson et al , 1949). Prominent among such factors are life situations which are either consciously or unconsciously threatening to the security of the individual (Fig. 17-1). Situations of pleasurable anticipation may also be associ*ated with tachycardia* and an increase in stroke volume It is as if bodily changes were occurring in preparation for exertion, e g , fighting, running away, or active participation in some pleasurable situation. When exercise is actually undertaken under such circumstances, the cardiovascular adaptation may be excessive or unduly prolonged during recovery, as if a much greater muscular effort had been anticipated

Cardiac Rhythm. It has been observed that arrhythmias, including paroxysmal atrial tachycardia, extrasystoles, atrial fibrillation, and even the more serious paroxysmal ventricular tachycardia (Fig 17-2), occur in association with troublesome events in the day-to-day ex-

periences of individuals who have no other detectable evidence of heart disease It would appear that this variety of disorders of cardiac rhythm may be precipitated by or possibly fundamentally related to threats arising out of the life situation It is certainly unnecessary to postulate underlying structural disease of the myocardium as a cause of arrhythmias even in the case of such *potentially* serious disorders as atrial fibrillation and ventricular tachycardia

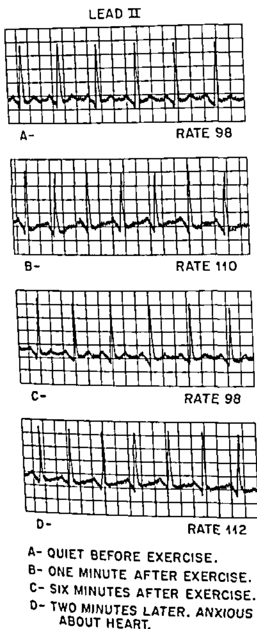


Fig 17-1. Marked depression of T waves in lead II of electrocardiogram. Essentially the same change was observed after exercise and during discussion of a stressful topic.

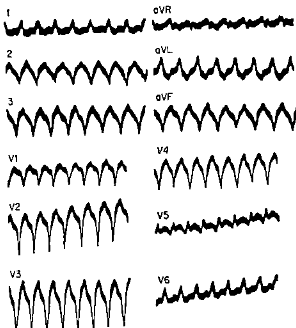


Fig. 17-2. Ventricular tachycardia occurring under stress in apparently healthy men without evidence of structural heart disease

The Electrocardiogram. Ordinarily when there are changes in the pattern of the electrocardiogram during exercise, the assumption is made that there is a disturbance of cardiac nutrition In the study of Stevenson et al., 19 patients displayed changes in S-T segments of T waves, to a degree considered significant according to the criteria of Master, following exercise performed during a period of stress. Six of the nineteen, or approximately one-third, failed to give any evidence of heart disease All had the symptoms previously described as characteristic of neurocirculatory asthenia and all but one were under 35 years of age The other 13 gave evidence of coronary arteriosclerosis In three patients, one with and two without other evidence of structural heart disease, exercise on a day of relative security and relaxation produced less change in the electrocardiogram than comparable exercise during anxiety.

In five of the six patients with neurocirculatory asthenia, and in all 13 of those with presumed coronary artery disease, it was possible to produce electrocardiographic changes during an interview covering pertinent personal problems, and without exercise or conscious anticipation of muscular effort The interesting

fact was that the changes induced during exercise were similar to those occurring during stressful interviews. In 14 of these instances, the heart rate immediately after exercise was nearly identical with that achieved during anxiety, and therefore the electrocardiographic complexes were fully comparable. In eight of these, the ECG during stress was identical with that following exercise. In four, the changes *during stress were greater than those induced* by exercise, and in two instances the changes were qualitatively different.

The changes observed in the ECG of one subject are shown in Fig 17-2 This patient, 32 years old at the time, had symptoms of palpitation and reduced exercise tolerance but gave no evidence of structural heart disease except for the ECG, which was normal at rest but in which T waves became inverted during exercise or during a stressful interview. Seven years later the patient still showed no further evidence of heart disease.

The mechanisms responsible for these changes cannot be stated on the basis of the data at hand. They may include coronary ischemia or perhaps merely sympathetic stimulation The interesting thing is that the changes with stress resulting from threats, symbols, or interpersonal relations are often similar to those following exercise

This information is in keeping with the general concept *that man during stress may react with his cardiovascular apparatus as if he were about to engage in strenuous muscular activity without any actual awareness of anticipating exercise.* Thus the electrocardiogram recorded during severe anxiety in a man with suspected coronary artery disease must be interpreted in the light of these findings Although the changes may be quickly reversible and may not always be of such grave import as is ordinarily thought, the possibility that repeated or sustained situational stress may lead to irreversible changes must be taken into consideration in planning therapy.

Congestive Heart Failure. As already pointed out, there is good evidence that mechanisms responsible for the retention of salt and water are connected with and responsive to impulses from the interpretive areas of the brain. Thus is provided a mechanism for either aggravation or mitigation of the manifestations of congestive heart failure in those patients with already impaired cardiac function. Experimental studies along this line have not been carried to the point of delineating to what extent such effects may be relevant to the bedside care of patients

PERIPHERAL VESSELS

Many important disturbances involving peripheral vessels are not customarily classified *among cardiovascular disorders These include* vascular headache, Raynaud's syndrome, hives, eczema, and various disorders of mucous membranes. The vasomotor mechanisms which appear to be responsible for these phenomena have been shown to be set in motion by a variety of stimuli, including situations or events which have a threatening significance to the individual.

Two familiar syndromes, migraine and Raynaud's disease, provide examples of vasomotor alterations in regional arteries which produce widely different symptoms. Both appear to be related chiefly to the attitudes and personality adjustment of the affected individual.

Ischemia and Tissue Damage. One way in which actual tissue damage may occur in response to changes in the function of peripheral blood vessels is through ischemia secondary to arterial constriction. It is well known in *Raynaud's syndrome,* for example, that damage to or loss of terminal phalanges may follow prolonged or persistently recurrent attacks.

In *migraine,* permanent ischemic damage to the brain has been shown to result from the preliminary vasoconstrictor phase when it has been exaggerated in degree or duration (Dunning et al.). *Cerebrovascular accidents* have been described in young individuals during periods of stress, and special proclivity for cerebral vascular contractility has been observed in such subjects using angiocardiographic techniques (Seidenberg et al.).

Tissue Damage Associated with Engorgement and Hyperemia. During the vasodilator phase of *migraine,* tissue damage may also occur. Subcutaneous extravasation of blood has been observed in an area where no mechanical trauma had been applied but where there had been extreme vasodilatation of a branch of the superficial temporal artery during an unusually intense migraine headache (Wolff et al).

The hazards of sustained engorgement of tissue, especially mucous membranes, include

a lowering of pain threshold and an increase in tissue fragility. In experiments on the stomach of a fistulous subject, it was repeatedly observed that noxious stimuli which did not induce pain when applied to the mucosa in its usual state did so when the membrane was in a state of sustained hyperemia and engorgement (Wolf et al). Likewise, relatively minor traumas, such as striking the membrane with a blunt glass rod or drawing a square of gauze over it, failed to produce a visible lesion when the membrane was in its usual state, but such maneuvers produced small hemorrhagic spots and erosions when they were applied to the *chronically* engorged mucosa. Often, in fact, small eroded areas appeared, apparently spontaneously, during a bout of unusually vigorous motor activity when the gastric mucosa was especially engorged

Thrombophlebitis and Phlebothrombosis. The work of Schneider et al has indicated a connection between certain types of emotional stress and intravascular clotting. He found in vitro an increase in blood viscosity with shortening of clotting time during circumstances productive of anxiety and resentment. In a group of patients with thrombophlebitis he was able to correlate clinical exacerbations with both the in vitro tests and the occurrence of conflict situations.

Atherosclerosis. There is renewed interest in the metabolism of cholesterol because of the possibility that atherosclerosis may be a nutritional disturbance of either intrinsic or extrinsic nature. Other factors which have been thought to be implicated are infection, climate, and glandular imbalance There is also growing interest in the relationship of vascular degeneration to stressful circumstances in our lives "Wear and tear" have for years been thought to underlie the pathogenesis of atherosclerosis and the disease states which are attributable to it, but the nature of the "wear and tear" has never been clearly defined So far, only fragmentary data are available to relate life stress to lipoprotein metabolism but, as mentioned above, recent studies indicate that certain situations of stress may be associated with a substantial rise in the level of blood cholesterol and an increase in lipoproteins of the S_f 12 to 20 category The relevance of such changes to the atheromatous process has, of course, not been established In this connection, the experimental findings of Cathey et al. have been reinforced by the observations of Groover, who found major rises in blood cholesterol in Air Force executives under stress. His data suggest that stress may be more important than diet in regulating cholesterol levels. However, these findings require confirmation.

Systemic Hypertension. It is an old observation, and very easily confirmed, that patients with essential hypertension, and normal subjects as well, display an increase in arterial pressure when brought into certain situations involving threats to their personal security. The pertinence of these responses to the initial causation or ultimate perpetuation of sustained arterial hypertension, however, *is not established* The investigator who studies hypertension is handicapped by the lack of relationship between level of the blood pressure and the presence or absence of symptoms, as well as the lack of uniformity and predictability of the natural course.

It has been shown, however, with appropriate documentation, that hemodynamic changes producing elevated arterial pressure, reduced renal blood flow, and increased blood viscosity occur as a part of an individual's adaptation to problems and challenges in his daily life (Wolf et al) Special attention has been directed to two contrasting patterns of hemodynamic adjustment which occur alike in hypertensive and normotensive individuals under stress One pattern appears to be identical with the "exercise" pattern, which is characterized by an increase in blood pressure explained by a rise in stroke volume without elevation of peripheral vascular resistance. The other pattern resembles that encountered in injury or hemorrhage. It is characterized by an increase in blood pressure attributable to an elevation in peripheral vascular resistance without a rise in stroke volume. When observed during interviews [illegible]
flicts,
manife[illegible]
tively [illegible], while the latter ("high resistance" pattern) was more often encountered with a calm exterior and evidence of suppression or repression of emotion.

In essential hypertension, there occurs a sustained increase in peripheral resistance without a rise in stroke volume There is, however, no significant difference between hypertensives

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2

Neurocirculatory asthenia

ARTHUR A. MILLER

This is a disorder characterized by many and varied symptoms (and few signs) referable to the cardiovascular system. It is not usually accompanied by structural damage to the heart, although at times this clinical syndrome may be superimposed upon organic cardiac disease. The most prominent symptoms include dyspnea, palpitation, left thoracic pain, nervousness, fatigue, dyspepsia, spells of dizziness, and "anxiety attacks." Friedberg states that what he designates as "neurocirculatory asthenia" or "cardiac neurosis" refers to "an ill-defined syndrome of psychogenic or neurogenic origin often mistaken for organic heart disease and characterized by dyspnea, precordial pain, palpitation, exhaustion, and a general incapacity or inefficiency in adjusting to physical or emotional strain." According to Walker, it occurs in 10 to 50 per cent of patients who visit cardiologists. It is thus a clinical syndrome of sufficient frequency and importance in clinical practice to deserve careful consideration of the mechanisms involved (somatic and psychological) in order to clarify diagnostic and therapeutic approaches.

Classical descriptions of this syndrome date from the American Civil War. During subsequent decades, particular attention has been given to this disorder in military situations. An increasing awareness of this problem in civilian life has, however, developed. Hartshorne (1864) described cases of "muscular exhaustion of the heart." DaCosta (1871) described the *irritable heart* and indicated recognition of the manifestations being due to a functional cardiac disorder. During World War I, a so-called "disordered action of the heart" or *soldier's heart* was described. Lewis (1917) designated the condition as *effort syndrome*. During World War I, a team of American Medical Reserve officers studied this condition in England and called it *neurocirculatory asthenia* (NCA) (Oppenheimer et al.). During and subsequent to World War II, there have been a number of papers on this disorder. Subsequent studies reflect efforts at more detailed clarification of the clinical manifestations and, quite significantly, attempts to integrate psychiatric observations.

From the foregoing and from the title of this section, it is apparent that the terminology applied to this disorder is not precise. There is no one designation which is consistently used and in the literature they seem to be used interchangeably. Cohen lists a number of terms, used in medical and neuropsychiatric literature and practice, to refer to a disorder with the above-described symptoms. These terms include neurasthenia, anxiety neurosis, neurocirculatory asthenia (NCA), nervous exhaustion, DaCosta's syndrome, effort syndrome, irritable heart, soldier's heart, somatization psychogenic cardiovascular reaction, somatization psychogenic asthenic reaction, anxiety reaction, vasomotor neurosis, névrose d'angoisse, personalities with mixed psychic and physical anomalies, and constitutional liability with tendency to functional disorders of specific organ systems. He states that, "the various terms used probably reflect more the special interests and theories of the various observers rather than a diversity of clinical disorders." This would certainly seem to be the case. With increasing understanding of the

and normotensives in their reaction to short-term stressful situations. Neither is there any correlation between an individual's response to interview and his reaction during a cold-pressor test, or between the type of vascular reaction to stress and the degree of vascular damage revealed by the eye grounds, heart size, or kidney function.

Further experimental studies have shown that the renal vasculature shares in the circulatory response to stressful events in the life situation. A decrease in effective renal plasma flow and an increase in filtration fraction occur in both hypertensive and normotensive subjects during a discussion of pertinent personal conflicts.

It is particularly notable that the mechanisms of the vascular apparatus responsible for raising the blood pressure in response to symbolic stimuli are not impaired by thoracolumbar or even "total" sympathectomy. Either the "exercise" or "high resistance" pattern may still occur, although there is no longer evidence of associated reduction in renal blood flow. It is conceivable that the loss of renal vasoconstrictor activity may protect the kidneys and thereby have a salutary effect on the course of essential hypertension. Perhaps it may be a factor in the apparent increased survival of sympathectomized patients even when there is no notable reduction of arterial pressure.

The significance of all these findings is not clear but there is nothing incompatible with the view that the *life adjustments in individuals with essential hypertension initially involve renal ischemia which may in turn set off a variety of endocrine and other humoral mechanisms with the ultimate development of irreversible tissue damage.* In any case, it is clear that stressful life experiences are sufficiently prominent, among stimuli which may elevate arterial pressure, to warrant their serious consideration in the clinical management of patients with essential hypertension. The evidence of emotional restraint and the calm exterior often displayed by these patients make it necessary for the physician to exercise special diligence and skill in uncovering meaningful life experiences and the attitudes and reactions associated with them.

A study of personality adjustment among the patients with hypertension does not delineate any characteristic personality "type," but yields strikingly similar data in regard to values, attitudes, and way of life. By and large, the hypertensives had grown up feeling the need to excel but at the same time to avoid conflict or too vigorous self-assertion. These strivings, often opposed, lead frequently to dilemmas and are manifested by wary, tentative, and noncommittal attitudes with respect to important interpersonal relations and major endeavors in life.

The results of therapeutic studies in essential hypertension will, of course, continue to be difficult to evaluate until methods are worked out to permit appraising the seriousness of essential hypertension and predicting its course. With all these limitations in mind, there is evidence enough to warrant the clinician's taking a serious interest in the background, life experience, and attitudes of his patient in the hope of helping him to a more constructive adjustment.

SUMMARY

A wide variety of vasomotor and hemodynamic disturbances in man have been examined from the standpoint of their relation to adverse or threatening life experiences. It would appear that cardiovascular functions in general are highly responsive to meaningful events and that a host of arrhythmias and peripheral vascular disorders may arise largely therefrom. The various hemodynamic mechanisms have been shown to respond to situations of which the force derives from their meaning to the individual; they respond to tangible stimuli in much the same way.

2

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From the foregoing and from the title of this section, it is apparent that the terminology applied to this disorder is not precise There is no one designation which is consistently used and in the literature they seem to be used interchangeably. Cohen lists a number of terms, used in medical and neuropsychiatric literature and practice, to refer to a disorder with the above-described symptoms These terms include neurasthenia, anxiety neurosis, neurocirculatory asthenia (NCA), nervous exhaustion, DaCosta's syndrome, effort syndrome, irritable heart, soldier's heart, somatization psychogenic cardiovascular reaction, somatization psychogenic asthenic reaction, anxiety reaction, vasomotor neurosis, névrose d'angoisse, personalities with mixed psychic and physical anomalies, and constitutional lability with tendency to functional disorders of specific organ systems He states that, "the various terms used probably reflect more the special interests and theories of the various observers rather than a diversity of clinical disorders" This would certainly seem to be the case With increasing understanding of the

psychiatric aspects of this disorder, there have appeared terms consistent with this point of view, i.e., anxiety neurosis, anxiety state, cardiac neurosis, somatization psychogenic cardiovascular reaction, somatization psychogenic asthenic reaction. Some authors use the term neurocirculatory asthenia when "constitutional" factors seem to predominate and anxiety neurosis when psychological factors seem to predominate (Miles and Cobb, Oppenheimer). Oppenheimer, who coined the term *neurocirculatory asthenia* but sees the disorder as being a variant of anxiety neurosis, recommends retention of the above term since it is noncommittal and carries no connotation which will harm the patient so afflicted. Weiss (1939), on the other hand, feels that the term neurocirculatory asthenia does more harm than good, that it calls attention to a part of the disorder, that it implies that the circulation is at fault, that it confuses the patient, and often leaves the physician to feel that he understands the disorder because he has given it an imposing name. He recommends that "since neurocirculatory asthenia does not exist without neurosis or character disturbance, I suggest that we call it that, using the proper psychiatric designation, and adding qualifying terms if necessary." It is apparent that there is no term which adequately designates the total nature of this disorder. Weiss' point of view seems particularly pertinent if we remember that psychiatric designations do not exclude awareness of the contribution of "constitutional" or somatic factors in the origin of "psychiatric" disorders

Thus far in this chapter, it has been indicated that emotional factors must be seriously considered to gain any real understanding of this disorder. Throughout the pertinent literature, including the early description by DaCosta, there has been greater or lesser awareness that emotional factors play an important role. Concomitant with the development of psychodynamic understanding of anxiety, including its psychological and somatic manifestations, its psychological significance, and the psychological defenses brought to bear against it, there has been a commensurate evolution of understanding of the role of emotional factors in this disorder Despite the advance of understanding in this direction, there have been differing points of view as to the relative importance of the role played by the emotions. The author will, subsequently, consider psychological understanding relative to this disorder, but let us indicate, briefly, some representative points of view on this matter. Friedberg says that this disorder is not a nosologic entity, that "it is nothing more than a moiety of the more generalized picture of psychoneurosis, which, in the cases under discussion, chances to assume entirely or predominantly the garb of cardiac or circulatory symptoms. Hence, the term 'cardiac neurosis.'" Cohen et al, who have published several authoritative papers on this disorder, are considerably more reserved when it comes to the consideration of emotional factors. Their clinical descriptions appear to be essentially those of psychoneurosis. They use the term neurocirculatory asthenia as being synonymous with anxiety neurosis, neurasthenia, and effort syndrome. They say that they are "unable to distinguish between patients with neurocirculatory asthenia as diagnosed by cardiologists and those with anxiety neurosis and neurasthenia as diagnosed by psychiatrists." They, however, state that "a crucial causal relationship of this disorder to life situations and emotion-provoking situations has neither been proven nor disproven." They exclude a psychodynamic approach as being unscientific and believe that no techniques have been developed as yet to permit conclusive observations concerning the exact relationships, if any, of life situations and emotion-provoking situations to this disorder. Miles and Cobb believe that "unless one makes some attempt, not only to measure the constitutional or physiologic factors, but also to understand the psychodynamics of the illness and of the therapeutic processes as well, it seems unlikely that even the most objective and scientific investigations can prove fruitful." Oppenheimer sees the disorder as a variant of anxiety neurosis. Walker believes that physicians are dealing, not with heart disease, but with persons who complain of their hearts Others (Wittkower et al; Wood) consider emotional factors of major importance for the understanding of this syndrome

CLINICAL MANIFESTATIONS

This syndrome is said to occur more in women during peacetime while, during wars, there is a higher incidence in men There appears to be a rather high *familial incidence,*

and it has been stated that tall, slender individuals, and those engaged in occupations requiring prolonged concentration and anxious tension or physical strain, especially if there is an element of danger, are more prone to develop this syndrome than others It has been said that *infections, physical exhaustion, nervous prostration,* or *anxiety* can be accompanied or followed by NCA symptoms out of proportion to the original cause. The emotional significance of these experiences is probably more important in producing the syndrome than is the direct effect of these conditions The age incidence seems to be mainly between 20 and 40 years but it occurs at any time of life

Symptoms. DYSPNEA. This is the commonest and most distressing symptom It is characterized *mainly* by an inability to take a breath or a satisfactory breath. *Irregular, deep, sighing respiration* can be seen, for instance, on a BMR curve. Even at bed rest, there may occur an inability to take a deep breath, and there is not the panting such as follows exertion The incidence and degree of dyspnea is disproportionate to the degree of exercise and objective disturbance of ventilation. A so-called *hyperventilation syndrome,* i e., an outburst of dyspnea and tachycardia has been described There may be a psychogenic expression of a *fear of suffocation* and there may be *claustrophobia* Accompanying the respiratory difficulty may be *tachycardia, sweating,* a feeling of *anxiety, giddiness,* and, at times, *tetany* may result.

PRECORDIAL PAIN The pain may be either sharp, dart-like, intermittent, piercing, transient, and localized about the left nipple, or continuous, dull, and poorly localized in the left anterior hemithorax or substernal region. It is unrelated to effort, but sometimes occurs after tiring exertion Characteristically, unlike the pain of coronary heart disease, it does not compel the patient to stop activity nor does it seem to be relieved by rest There may be local tenderness in the precordium. A physiological mechanism for this pain and tenderness has been described (Wood, Friedman, 1948), apparently related to the effect of thoracic rather than diaphragmatic breathing

PALPITATION There is an awareness of the heart beat in the absence of arrhythmia, although often there may be tachycardia and forceful cardiac pulsations. The cardiac discomfort, pain, and intense anxiety may at times be accounted for by occasional premature beats or paroxysmal tachycardia.

FATIGUE. This can be chronic or occur in attacks It may consist of a sense of fatigue *upon arising in the morning* which diminishes during the day (it is to be noted that this symptom is not uncommon in psychological depressive reactions); or else, it may be a profound sense of exhaustion *following moderate physical exertion.*

PSYCHIC SYMPTOMS These are common and characteristic, and along with anxiety include phobic reactions, depressive reactions, and hypochondriacal symptoms A variety of other symptoms are observed and described. They include dizziness, sweating, cold clammy palms, nervousness, tremor, *headache,* flushing, frequent micturition, *insomnia,* paresthesia, faintness, diarrhea, difficulty in concentration, indecision, impairment of memory, and a tendency to mental, emotional, and physical *apathy.* Almost any bodily system may be involved in the symptomatology along with the cardiorespiratory system *In general, the symptoms appear related to "peripheral sympathetic manifestations" or "autonomic imbalance" and consequently any of the multitude of symptoms characteristic of this physiological state may appear.*

Objective Signs. Whereas the symptoms are multiple and varied, objective signs are not an especially prominent part of this clinical picture. As regards this condition per se, there are no objective signs of organic heart disease, but the disorder may occur with any form of structural cardiac pathology At times, the discovery that one has an organic heart disease may be followed by an increase in symptomatology, of the nature of NCA, which is not accounted for by the organic pathology. There may be *tachycardia,* which is related not to effort but to emotional attitudes There may be a mild fever, which is rarely over 100 5°. It has been observed that blood lactate is higher in NCA during moderate exercise than in control subjects Exercise may cause a rise in pulse rate greater than that in healthy subjects and with an abnormal delay of return At times, arrhythmias may be observed Basal metabolic rate, radiography, and ECG are normal, except for changes due to hyperventilation.

(Luisada, Friedberg, Cohen et al ; Walker.)

THE ROLE OF PSYCHOLOGICAL FACTORS

Anxiety. Advances in understanding of the psychobiological phenomenon of anxiety have provided a frame of reference for understanding such psychophysiological disturbances as the disorder now under consideration (Grinker and Robbins). In 1894, Freud described the symptomatology of *anxiety neurosis.* This clinical state included "general irritability, anxious expectation, anxiety attacks proper, rudimentary anxiety attacks (e.g., disturbances of heart action, disorders of respiration, sweating, tremors, ravenous hunger, vertigo, vasomotor neurasthenia, paresthesias), pavor nocturnus of adults, certain phobias" This phenomenological description of anxiety still holds true today. At that time, Freud considered that this phenomenon resulted from a transmutation of energy, i.e., if there were no capacity for outward expression of impulses (the blocked energy of sexual impulses, for instance), it became converted into anxiety. In subsequent developments of his theory of anxiety, Freud saw anxiety, not as a transmutation of energy of sexual impulses, but as a warning signal to the organism of some kind of danger

In the face of a situation of danger, one experiences a state characterized by psychological and physiological features, a sense of dread and foreboding, and the many physiological responses related to reactions of the vegetative nervous system Cannon described these physiological responses as preparing the organism for action in either fight or flight at a time of danger This, of course, is a necessary, healthy, warning and alerting response When, however, the response is greater than the external danger seems to require and when the response occurs without the presence of an apparent external danger, there exists an anxiety reaction with pathological implications Frequently, such anxiety occurs in the face of an individual's internal psychological conflict over impulses and thoughts which are psychologically unacceptable to him. When an apparent external danger is present, the response is usually designated as *fear;* when the response is disproportionate to the external danger or occurs without the presence of an obvious external danger it is designated as *anxiety* The actual psychophysiological responses of fear and anxiety are difficult to differentiate.

Individuals vary in the way in which they experience anxiety. Anxiety may be represented by parts of the total psychophysiological phenomenon. "Anxiety in the adult activates certain visceral patterns which are specific to the individual, no matter what the stress. Each one has his particular way of feeling anxious. Some variations include sinking abdominal sensations, diarrhea, vomiting, dyspnea, sensation of a lump in the throat, etc. Out of the generalized infantile precursors of anxiety, each person seems to have been conditioned to certain fragmentary visceral patterns which for him become accurate and faithful harbingers of intra-psychic danger" (Grinker and Robbins). In the light of this, it can be seen where cardiorespiratory symptoms can be representative of anxiety in a particular individual. Either these symptoms, cardiac and respiratory, may be the only representatives of anxiety or they may be the only evident ones, depending on the particular inclinations of the observer.

Anxiety is recognized as being common to all the neuroses The particular neurotic reaction, in fact, is considered to be the resultant of the types of psychological defense used to ward off the experiences of anxiety An individual may experience episodes of anxiety as such and thus be suffering from an anxiety neurosis Development of defenses against such an experience, varying with the types of defense, may result in such neurotic reactions as phobias, hysterical conversions, obsessive-compulsive neurosis, depression, and hypochondriacal reactions. In any of these conditions, there may be an array of symptoms which would meet the criteria of "neurocirculatory asthenia."

Psychogenic Factors and Constitutional Factors. Miles and Cobb emphasize multiple causative factors in disease, i.e., any particular disease state may be the result of the interplay of factors which they call (1) genogenic-hereditary, (2) chemogenic, (3) histogenic-structural, and (4) psychogenic. In the case of neurocirculatory asthenia, they consider a continuum, at one end of which are those cases primarily due to, for instance, genogenic and chemogenic factors· those patients who have evidence of a constitutional physiological deficit; and, at the other end of the continuum, those instances wherein psychogenesis is primary. Most patients fall between the extremes

of this continuum. Ross studied a group of neurocirculatory asthenia patients with the *Rorschach test*. He found that these patients presented features similar to those of psychoneurotics of other types. The NCA patients showed a tendency to give up in the face of difficulties as well as an obsessional conscientiousness which made their life problems appear more difficult to them than was necessary. He recognized cases of two general types (1) of long-standing nature and (2) of recent onset, and considered that the first type was possibly due to constitutional factors whereas the latter might be due more to current psychological stress. Jones and Scarisbrick delineated three groups of neurocirculatory asthenia patients.

1. Patients with poor physical endowment as the primary factor, these show effort intolerance since earliest recollection.

2. Patients similar to those in group 1 but differing in that they respond in a neurotic manner to their constitutional inferiority. In this group, there is a psychological origin but constitutional factors are basic. Emotional reactions that occur may assume any form, and the actual disability may be less than the person feels it to be.

3. Patients whose difficulties are primarily neurotic in nature. The clinical picture may be colored by constitutional factors but the latter are of secondary importance, or the clinical picture in this group may be wholly psychogenically determined.

There are a number of references in the recent literature wherein the role of psychological factors in this disorder is considered and documented (Oppenheimer, Walker, Weiss, Wittkower, Maloney, Kerr, Wood). Wittkower, studying a group of unselected soldiers with "effort syndrome," found none to be emotionally well adjusted and delineated five personality types among them. Wood emphasized that this syndrome is not a disease in itself and that it is a symptom complex usually occurring together with some psychiatric disease.

PHYSIOLOGICAL CONSIDERATIONS

Neurocirculatory-asthenic patients show responses which are quantitatively, not qualitatively, different from healthy subjects when exposed to various types of stimuli and stress (Cohen and White). The hyperthermia, giddiness, cardiovascular manifestations, respiratory manifestations, and "episodic neurogenic discharge," are said to be due to *hyperirritability of the sympathetic nervous system*, probably related to involvement of the hypothalamus (Friedman). There appear to be quantitative physiological differences between those patients with effort intolerance of lifelong duration and those patients who develop the disorder acutely under current stress (Jones and Scarisbrick). Patients with anxiety show a greater cardiovascular response to exercise than patients without anxiety (Stevenson et al.).

DIAGNOSIS

Diagnosis of this disorder depends, as does all diagnosis, on careful history taking and examination, followed by interpretation of the findings in the light of an understanding of the disease process and mechanisms. In this instance, particularly, an understanding of psychological phenomena and mechanisms—anxiety as a psychobiological phenomenon and defenses against anxiety—is particularly important for correct understanding, diagnosis, and treatment of this disorder.

Emotional disorders have their own distinct features that can be discovered by personality study and awareness of their manifestations. One can agree with Walker when he says that no greater blame should be attached to the physician who fails to make a physical examination than to one who fails to explore the mind. This point of view is particularly important in the type of disorder under consideration. It has been noted that the patient's choice of his presenting symptoms, psychological or physical, may determine whether the patient is referred to a psychiatrist or an internist. Depending upon the "prejudices" of the observer, the same disorder may be recognized as two different entities. The same patient may be diagnosed on successive hospitalizations as a victim of neurocirculatory asthenia, gastric neurosis, or anxiety neurosis, depending on the shift of emphasis on presenting complaints, all of which symptoms may be part of the total picture which are emphasized at various times. Exclusion of the existence of organic heart disease is an important diagnostic point. It is to be emphasized, however, that *neurocirculatory asthenia may exist when organic heart disease is also present,* in which instance there is no clear relationship between

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able psychotherapeutic help without referring the patient to a psychiatrist. In this group of patients, when they are confronted with acute stressful situations, handling of the problem as was suggested above can often help the patient to reach a more satisfactory level of functioning Some cases may require continuous emotional support which can be effected by periodic visits to the physician.

There are other cases which require referral to a psychiatrist. In some patients, who have been relatively intact psychologically prior to an acute stress, the reaction to stress may be of such intensity that the therapy requires the services of a psychiatric specialist The degree of psychopathology in many of the chronic cases may be such that handling of the acute problem or emotional support by the physician is not sufficient and the services of a psychiatrist are required.

Symptomatic therapy can be considered secondary but important in the handling of these cases This includes such measures as the judicious use of sedation, rest, and occupational therapy.

CARDIOVASCULAR DISORDERS OF PSYCHOTIC PATIENTS

The syndrome described and discussed in the earlier part of this chapter can occur in psychotic patients as well as in patients with various types of neurotic disorders and character disorders Anxiety and defenses against anxiety are at the center of all psychopathological phenomena, neurotic and psychotic The type of psychological defense used by the individual in order to avoid the experience of anxiety determines the type of pathological manifestations

Patients who are psychotic, neurotic, or "normal" can all, at various times, experience anxiety, which, as previously stated, can be represented mainly by cardiovascular manifestations Some psychotic patients are particularly vulnerable to the development of anxiety, because [illegible] def[illegible] [illegible] threatening to them

Certain features of the psychological defense manifestations in psychotic patients determine the character of the cardiovascular complaints found in such patients. The features of interest include the psychotic's break with reality, turning of interest from other people and things to oneself and one's body, delusions, and hallucinations (Fenichel). Somewhat schematically stated, the psychotic patient, being unable to integrate his feelings and impulses with the real world of people and things breaks with reality, withdraws into himself and, at times, substitutes for reality false thoughts, delusions, and false perceptions, hallucinations

Of particular clinical interest is the observation that at times a schizophrenic patient in the process of breaking with reality may present himself to his physician, preoccupied with bodily complaints. Along with any other system or part of the body, the cardiovascular system may be the focus of such complaints Having broken with reality and thereby being in a state with faulty "reality testing," the patient might elaborate otherwise insignificant bodily sensations into complaints which to the patient have the implication of somatic pathology A more or less tenacious hypochondriacal concern with bodily parts and functions may characterize the schizophrenic patient in the early phases of his break with reality, or, for that matter, at any stage of the disease process The complaints may take on the character of *somatic delusion* These may consist of complaints which are more or less obviously bizarre in nature At times, the exact content of the patient's thought may be somewhat difficult to obtain The patient, for instance, might present the idea that he must breathe in some peculiar manner and rhythm lest something happen to him, other people, or the world, or he might have such notions as that his heart is shriveling or breaking open or that his heart is in some bizarre location in his body Particularly important is that the physician be aware that *early manifestations of a schizophrenic breakdown may be characterized by the patient's preoccupation with somatic complaints*

There are reports in the literature on the relationship between psychoses and psychosomatic disorders (cf. summary of this subject by Ross, review of literature of the relationship between cardiovascular manifestations of a psychosomatic nature and psychoses by Miller and by Swartz and Semrad). There are studies that appear to indicate that psy-

the presenting symptomatology and the severity of the organic heart disease. The diagnosis, however, is not only by exclusion but by alertness to positive data supporting the psychological basis of the symptomatology. The decision to refer a patient to a psychiatrist for examination depends upon the training and ability of the physician in attendance, i.e., his awareness of, alertness to, and ability to handle psychological factors in disease.

The differentiation of this disorder from various medical illnesses is at times a problem. Patients at times may receive the diagnosis of tuberculosis, thyroid disease, cardiac disease including angina pectoris, "murmur," rheumatic fever, sinusitis, undulant fever, and, if the symptoms involve other systems, Ménière's disease, peptic ulcer or gastric neurosis, genitourinary disorders, or disorders of the nervous system

THERAPY

Therapeutic approaches to this disorder must be based on correct diagnosis and understanding. It is important to assess (1) constitutional (physiologic) mechanisms, i.e., patients with lifelong "low effort tolerance"; (2) long-standing psychological difficulties (that is, patients with a chronic psychological disorder who have a propensity for the development of anxiety and cardiovascular symptoms), (3) patients who up to the time of onset of symptoms have been relatively intact physiologically and psychologically but who have been confronted with a rather acute, stressful psychological experience with the development of anxiety and psychological defenses against this anxiety. Physiological, psychological, and environmental factors must be considered

In all cases, the physician must be aware that his initial and subsequent handling of the case can determine whether the patient is directed to the road to recovery or whether there is a tendency for the disorder to become fixed, intractable, and chronic. In other words, "*iatrogenic*" *factors* can foster neuroticism, which, in this instance, is manifested by cardiorespiratory symptoms A thorough history must be taken and a complete examination performed. Following this, the physician must, without equivocation, inform the patient that he has no organic cardiac disease, that he has an "emotional disorder" and that his heart is normal and there is no reason why anything should happen to it. It is very important not to give the patient the impression that, by making such a diagnosis, one considers him a second-rate individual and looks down on him. The therapy should not be complicated by giving the disorder a name which serves no purpose but to arouse the patient's anxiety and really does not explain the nature of the situation The physician's understanding and interest in the patient's symptoms should be communicated in the physician's words and manner.

Recommendation of *rest* should be very judiciously made, lest one foster a chronic neurotic withdrawal from a constructive solution of whatever problems have brought about the symptoms.

When constitutional-physiologic predispositions to the development of symptoms can be discerned, one has to consider with the patient the establishment of a regimen of activity which diminishes the stress to his physiological mechanisms.

It is in regard to psychogenic factors that more definitive therapeutic approaches can be made In those cases where it is apparent that there is a relationship between acute psychological stress and the development of symptoms, it is by no means necessary to refer all such patients to psychiatrists The nonpsychiatric physician can perform effective and important psychotherapy commensurate with his experience, interest, and effort toward doing so A patient who is struggling with a recent psychologically stressful situation can gain much from the doctor-patient relationship· (1) from the emotional support which derives from the very existence of such a relationship, giving someone with whom the patient can talk, (2) from intellectual support offering help in the clarification of the problems that confront him and a presentation of possible ways of solving them; (3) from an opportunity to ventilate his feelings about the matter; (4) from suitable environmental changes when they are indicated; and (5) from the opportunity to reinstate previous psychological defenses or, when possible, to reach a satisfactory, constructive solution of the problem.

In cases where there have been long-standing neurotic or psychotic difficulties, the nonpsychiatrist, again, can often be of consider-

able psychotherapeutic help without referring the patient to a psychiatrist In this group of patients, when they are confronted with acute stressful situations, handling of the problem as was suggested above can often help the patient to reach a more satisfactory level of functioning Some cases may require continuous emotional support which can be effected by periodic visits to the physician.

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Certain features of the psychological defense manifestations in psychotic patients determine the character of the cardiovascular complaints found in such patients. The features of interest include the psychotic's break with reality, turning of interest from other people and things to oneself and one's body, delusions, and hallucinations (Fenichel). Somewhat schematically stated, the psychotic patient, being unable to integrate his feelings and impulses with the real world of people and things breaks with reality, withdraws into himself and, at times, substitutes for reality false thoughts, delusions, and false perceptions, hallucinations

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choses and psychosomatic disorders tend not to exist together. Perhaps the best evidence of this nature has been presented in relation to asthma and peptic ulcer. In the realm of cardiovascular manifestations, a fair amount of attention has been given to the relationship between *blood pressure levels in psychotic patients* and a possible higher incidence of *rheumatic heart disease in "dementia praecox" patients.* The resultant of the several studies on blood pressure levels seems to indicate that elevated blood pressure is probably no less frequent in mental hospitals than in outside medical practice. Some studies, however, seem to indicate that schizophrenic patients tend to have *lower* blood pressure levels than do control subjects. This lower blood pressure level seems to be especially true of catatonic patients. Psychotic epileptics seem to be free from hypertension. There appears to be evidence for elevated blood pressure correlated with depressive and paranoid trends, apparently related to the inhibited aggression which characterizes these clinical states (Miller).

It must be emphasized, of course, that structural cardiac disease can exist in psychotic patients along with the possible disorders described above.

PART 18

Heart failure; Pulmonary edema

1

Experimental heart failure

WILLIAM F. HAMILTON

"Congestive failure" of the circulation is common in clinical medicine and growing more common. In veterinary medicine it is less common but is being recognized with greater frequency in dogs, particularly in spaniels Only recently has it been produced experimentally

THE REGULATIONS OF THE NORMAL CIRCULATION

In order to understand the mechanism of congestive failure, it is necessary to understand how the circulation is regulated and how the sequelae of cardiac weakness, valvular disorder, or overwork may give rise to the manifestations of pulmonary and systemic congestion which are known as "congestive failure" It is further necessary to outline how these manifestations are to be produced and modified experimentally

The circulation seems to be regulated by the peripheral arterioles rather than by the heart, the heart acting as the pump in the water works of a city, which keeps constant the pressure in the distributing system It is only when the well runs dry that the filling of the pump assumes critical importance In the normal circulation, the heart is supplied with venous blood in ample measure and by ingenious contrivance, so that it may pump twenty times the normal resting output and forty times that [illegible]

[illegible] To be specific, when a muscle becomes active, local mechanisms cause its blood vessels to dilate Again, when the room is warm, the skin arteries dilate reflexly. The resulting drop in blood pressure whips up the rate and the strength of the heart by way of reflexes which originate in the carotid sinus and the aortic arch These reflexes do not cause the heart to overdo because, when the blood pressure gets back to normal, these same reflexes put the brakes on the heart and open up arteriolar safety valves. In short, the cardiovascular regulation is engineered to maintain a constant distributing pressure no matter what the local demands may be.

The manner in which the heart does the increased pumping that serves increased activity is interesting and, in describing it, the author must break with tradition If the size of the dog's heart is measured radiographically in a carefully quantitated fashion it is determined (Hamilton et al, 1950, a, b), that, as it pumps harder and faster, it grows smaller The only clear correlation between heart size and any other cardiac function including stroke work, stroke volume, and venous pressure, *is between heart size and heart rate.* The faster it goes, the smaller it becomes In general, the faster it goes, the more work it does

At first glance, it would seem that this contradicts the classical principle of Starling's law of the heart This is not so Starling's principle (Part 2, Chap 6) was stated for conditions which rule out reflex and hormonal regulation Starling devised the heart-lung preparation so that these influences would surely be ruled out and came to the conclusion that, when the heart is considered as a simple isolated muscle, its pumping energies and its metabolism vary directly with its diastolic size. The more distended the heart, the more strongly it pumps and the more energy it releases However, if the heart is overdistended, the gain becomes a loss and the pumping weakens

The difference between the behavior of the heart in the normal animal and in the heart-lung preparation is, of course, the result of reflex and hormonal adjustments that protect the natural heart from the stress of dilatation, and the fact that the natural heart has a large volume of residual blood in its

cavities and can increase its stroke by *emptying* more completely as an alternate to filling to a greater diastolic size.

The fact that the natural heart is reduced in diastolic size under stress and differs in this respect from the isolated heart of Starling has been documented for the dog heart during exercise by Rushmer (1952, 1954) and for the human heart by Liljenstrand et al who showed that the heart of the individual when supine was larger than when he was doing exercise.

It is, of course, well known to clinicians that the *diseased heart* dilates and thus gains strength in accordance with the Starling principle. If the *dilatation is too great, the heart loses strength, again* in accordance with Starling's principle. This dilatation, however, is a mechanism of last resort, used only when reflex and hormonal adjustments have failed. The diseased heart meets stress by increasing its diastolic size, the normal heart by diminishing its systolic size This is done by reflex augmentation of the rate and strength of the contraction.

The only application of Starling's law that can clearly be made to the heart with all of its natural reflex controls was clearly put forth by *Henderson* and Prince long before Starling The two ventricles are, of course, controlled by the *same mechanisms* and neither can be stimulated separately by either reflex or hormonal agencies. The only way that either can carry an extra load or overcome an extra handicap is by gaining strength through the Blix-Starling mechanism, that is, by dilating to a greater diastolic size Henderson and Prince by ingenious experimentation showed that the filling and response curves of the two ventricles safeguarded the pulmonary circulation from being either depleted *or distended.*

CAUSES OF CONGESTIVE FAILURE

Backward Failure. In the pulmonary circulation within physiological limits, the above-described adjustment works very efficiently. *We all know, however, that, with pathological* handicap to the left ventricle, the needfully *perfect balance between the outputs of the* right and left ventricles can be preserved only at the expense of an abnormally high left atrial (and intrapulmonary vascular) pressure, the pressure that fills the left ventricle

The development of this high pulmonary vascular pressure leads to many of the clinical aspects of heart disease. The lungs become engorged and stiffer, so that the work of breathing is increased and respiration becomes dyspneic. Blood in the dilated heart and engorged lungs encroaches on the pulmonary air space and reduces the vital capacity. This blood increases the circulation time, and its pres may cause incipient pulmonary edema with familiar "moist rales."

This condition can be produced experi tally but, so far as the author knows, it n appears as a chronic condition in experime animals. Any condition which puts a suffi strain on the left heart will increase the i vascular pressure in the lungs. A typical *is an overdose of epinephrine.* Both pulmo arterial and pulmonary venous pressures alike and the difference between them les *There is no evidence of* pulmonary vaso striction, even when the drug has pa through the lungs on its first circulation. same dose of drug with nearly the same fect on the systemic pressure can be g with no rise in pulmonary pressure if the mal has suffered hemorrhage. The au thinks that, ruling out possible action on lung of irritant gases, pulmonary edema i ways due to the fundamental mechanism i trated here. The picture is one of a weake or overwhelmed left ventricle, back pressu the lungs, and filtration through the capilla and the condition can often be amelioratec venesection or by other measures, e g , v dilator drugs designed to reduce the load the left ventricle or lessen its effects, or the of alcohol fumes to lessen frothing of the ed fluid (Luisada, 1950).

Backward Failure in the Systemic Circ tion. There is doubt in the minds of phys gists that backward failure of the right h can occur, whether it is consequent to heart failure or is the result of initial inc petence of the right heart After epineph the systemic venous pressure changes slightly, even though the pulmonary vasc pressures are high and the left ventricle fers an acute dilatation. In contrast to pulmonary bed, the systemic bed is very pacious, particularly as to its venous port in order to distend it a large increase in bl volume is necessary. In addition, the heart self is dilated and contains a greatly increa amount of blood as compared to its nor state Not only are the blood volume venous pressure increased, conditions wh persist post-mortem, but also there is a g increase in the interstitial fluid volume.

This plethora and dropsy can only be

plained on the basis that there has been a long-standing imbalance between the intake and output of salt and water. The kidney is the organ controlling the output of salt and water and it seems clear that the fault lies in this organ

The kidney may retain salt and water in amounts to form edema for any of three causes: (1) deviation of fluid into the interstitial spaces before it can get to the kidney; (2) alteration in renal hemodynamics so that filtration is so small that resorption of filtered sodium and water occurs, and (3) augmentation of tubular resorption of sodium and water by hormonal or other stimulation.

Prerenal deviation due to high venous pressure is the traditional explanation for edema As seen above, the initial stages in the rise of venous pressure cannot be explained in this manner Nor is there any necessary correlation between the development of edema and the level of venous pressure. Altschule and Blumgart believe that, in tricuspid stenosis, venous pressure is elevated without edema, and Altschule (1954) indicates that, particularly in mitral stenosis, edema may develop with normal venous pressures Merrill (1949) finds that edema precedes the rise in venous pressure as heart failure develops, though this has been questioned

The causal relation of high venous pressure to experimental ascites is moot. Davis et al (1953, 1955) believe that ascites develops only when the pressure of the inferior vena cava is high Others report ascites in the absence of signs of chronic passive congestion and with the pressure of the inferior vena cava exceeding the (high) intraabdominal pressures There seems to be an equivocal relation between ascites and high venous pressure in experimental tricuspid stenosis and Waugh has shown that, during the onset of ascites from vena cava constriction, 10 days elapse, in which the caval pressure is high, before ascites develops. The trigger seems to be the exudation into the abdomen of a small amount of ascitic fluid of high protein content. Ascitic fluid in the dog has a protein content 1 to 1 5 per cent lower than plasma while, in man, the difference is much greater Barger finds significant sodium retention in animals who have received slight valvular damage, this was not sufficient to produce a rise in venous pressure, even though the pressure was high when frank congestive failure developed.

This equivocal relation between edema production and venous pressure is to be expected on physiological grounds There is a perfect balance between outward filtration at the arteriolar end of the capillary and inward diffusion at the venous end of the capillary but this is precarious and can be upset by very small changes in venous pressure (even by drinking a glass of water, which passes out through the capillary with infinitesimal changes in venous and osmotic pressures).

These considerations lead to the thought that *the rise in venous pressure is coincident with edema rather than its cause,* and to look elsewhere for the underlying basis. It is well known that, in nephrotic episodes, oliguria will lead to edema and that for unknown causes this may be followed by diuresis and evacuation of edema with no change in venous pressure Similarly, bed rest may cause diuresis in cardiac patients with no lowering of venous pressure. This and other evidence points to the causal role of a possible upset in renal function in the edema of heart failure.

Renal Function and Edema Production. Renal function may be disturbed in heart failure by a simple change in renal hemodynamics or by a stimulation of tubular resorption Merrill showed that glomerular filtration was greatly reduced in congestive failure He thought that the small amount of filtrate was nearly cleared of sodium and water by the obligate function of the proximal tubule Against this is the fact that, when patients come out of decompensation, they usually do so with a continued low filtration rate, such changes as do occur being random; this fact has been confirmed by many workers In experimental animals, it has been shown that circulatory handicap may result in increased reabsorption of sodium and water with filtration remaining within normal limits This is true temporarily when the renal vein is constricted, and permanently when the inferior thoracic vena cava is constricted, or when a dog is affected with mitral, pulmonic, or tricuspid stenosis

Stimulation of Tubular Resorption. It seems doubtful from the above that the edema of heart failure can be explained as the result

of prerenal deviation of fluid or as a result of changes in renal hemodynamics. It remains, therefore, to inquire into the possibility that *the salt and water are retained as a result of overstimulating the tubular resorptive function.* Raising the pressure in one renal vein causes a unilateral increase in tubular resorption of these substances with no other changes in renal function or capacity. However, since this is only a temporary response and does not lead to ascites, the permanent ascites which results from the other, above-mentioned handicaps requires further analysis.

Since the last century, clinicians have known that *a low-salt diet was good for dropsical patients.* The ascites of experimental circulatory handicap is also dependent upon sodium. This ion can be withheld from an ascitic dog either by the careful control of the diet or, much more conveniently, by the use of ion exchange resins (Carbo-resin). When sodium is withheld for a few days, a diuresis sets in and the ascitic fluid is promptly evacuated. The animals can be kept apparently normal for weeks under this treatment, only to regain their ascites as soon as a normal diet is reinstituted.

It is also recognized clinically that the *withholding of water is not helpful in treating cardiac dropsy.* Nonetheless, the rarity of cases of diabetes insipidus with congestive failure leads one to wonder if the two diseases are not incompatible and whether water might not be retained, holding sodium, by means of the antidiuretic hormone In order to test this, Waugh produced diabetes insipidus in a number of dogs by the usual operation. Some were ascitic in spite of the fact that they were urinating four to ten times the normal volume In others, the circulatory handicap produced ascites even in the presence of well-established diabetes insipidus.

Adrenal Hormone. An important step in the further analysis was taken by Davis (1953), who showed that the ascites which resulted from inferior vena cava constriction could be aborted or evacuated by *adrenalectomy* The stimulus which caused the kidney to avidly resorb sodium was evidently secreted by the adrenal gland since removal of this gland promoted loss of retained fluid. The substance secreted by the adrenal (probably *aldosterone*) was no longer available and had to be replaced by administration of either a high-salt diet or DCA or other salt-retaining sterones, in order to maintain salt balance.

These observations were extended (Hamilton, 1954) to the ascites following experimental mitral stenosis and to that following experimental tricuspid stenosis (Brown et al, 1956). The same observations were made in experimental pulmonary stenosis (Davis et al, 1955) and it was shown that the strength of the right ventricular beat, the cardiac output, venous pressure, and renal functions, were restored toward normal by digitalis. This last observation makes it clear that the main action of digitalis on the dilated heart is to strengthen the myocardium, in spite of the fact that it interferes with pumping in the normal heart.

If aldosterone causes the kidney to retain salt and water to form cardiac ascites in the dog, and by inference edema fluid in man, the question remains. what is the stimulus which produces this activity in the adrenal gland? This is indeed puzzling. The administration of the cortisone-producing pituitary hormone (ACTH) or of cortisone itself, will not cause any significant retention of salt or water in dogs (Howell et al., 1955). Hypophysectomized dogs respond normally to feeding excess salt and to withholding salt, but not to circulatory handicap Thus Craig and Wetzel, as well as Davis, and Waugh and Hamilton, have shown that ascitic dogs promptly lose ascitic fluid when the pituitary gland is removed The identity of the stimulus which causes the pituitary-adrenal complex to become active in response to circulatory handicap remains to be seen.

To summarize this review on experimental congestive failure of the circulation, it would seem that simple backward failure of the left ventricle is an adequate description of the pulmonary congestion which accompanies the disease but the retention on the systemic side of the circulation of intravascular and extravascular fluid, together with the rise in venous pressure, is much more complex. Renal retention of salt and water is a necessary step in the mechanism This retention is not the simple consequence of low filtration but must also involve stimulation of tubular resorption of salt and water which is probably hormonal The antidiuretic hormone of the posterior pituitary gland does not seem to be involved in

the production of ascites The adrenal gland plays an important role in the vicious cycle, as does, in all probability, the anterior pituitary. The actual mechanism of the initial stimulus and many of the connecting links are unknown

The biological meaning of this response is puzzling It cannot be a homeostatic response since the retention of water and sodium by an organism already inundated by salt water is hardly a regulatory response. It is better to regard it as a response which meets adequately an acute emergency but is badly adjusted to a chronic diseased state The conservation of body fluid and sodium is easily recognized as important in preparation for the violent activity displayed in meeting an emergency. Heat can be liberated, and the circulation maintained, if fluid is in adequate supply. Moreover sweat involves the loss of salt and anoxic or traumatic cell damage, an escape of potassium into the extracellular fluid compartment. Since aldosterone has the effect of conserving sodium, and with it water, as well as releasing potassium, Meneely suggested that its emergency secretion fits neatly into the biological picture Its continuous secretion in a chronic disease that simulates an emergency situation can thus be explained on Darwinian grounds even though it is not homeostatic.

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Cardiac output and venous return in heart failure

ARTHUR C. GUYTON

Because the term "heart failure" can be defined in several different ways, it is impossible to discuss cardiac output and venous return during failure without first defining the term as it will be used in this chapter. One definition of heart failure is simply that *the heart fails to pump all the blood returning to it from the systemic circulation* According to this definition, the heart itself may be perfectly normal but still cannot pump all the blood simply because flow through the systemic circulation is unusually rapid (*relative heart failure*). Another definition of heart failure is that *the actual pumping effectiveness of the heart has been impaired* (*absolute heart failure*) The present discussion will employ this latter definition However, later in the chapter, the factors that cause high cardiac output in "high output failure," in which the heart itself is either completely or nearly normal, will be discussed separately.

QUANTITATION OF FAILURE

One cannot determine how severely the heart is failing by simply measuring the cardiac output because, even a normal heart which does not receive an adequate venous return of blood, may pump only a few milliliters of blood per minute. In this instance, the heart would not be failing in the least. On the other hand, it is not possible to quantitate the degree of heart failure by simply measuring the venous pressure because the venous pressure can be elevated even in the presence of a normal heart if blood is flowing into it at an excessive rate Consequently, to quantitate the degree of failure, one must speak in terms of the ability of the heart to pump blood at many different right atrial pressures (Sarnoff).

Figure 18-1A illustrates function curves called "cardiac output curves" which depict the pumping ability of a normal heart and of hearts whose pumping effectiveness has been depressed 25 per cent, 50 per cent, and 75 per cent, respectively. This graph depicts the amount of cardiac output which could be expected from the respective hearts at each right atrial pressure In the normal heart the cardiac output at each right atrial pressure is greater than that of any of the failing hearts. The heart that has lost 25 per cent of its pumping effectiveness will pump only approximately 75 per cent as much blood at each right atrial pressure as that pumped by the normal heart Correspondingly, the hearts that are failing 50 and 75 per cent pump only one-half and one-fourth as much blood as does the normal heart at each given right atrial pressure. Thus it can be seen that the degree of cardiac failure can be quantitated by means of cardiac output curves Conversely, one can estimate the degree of failure of a given heart if both the cardiac output and right atrial pressure are simultaneously recorded. For instance, if a person's resting cardiac output is 5 liters/min and his right atrial pressure is 0 mm Hg, then the point described by these coordinates in Fig 18-1A lies on the curve of the normal heart, which means that his heart is operating normally On the other hand, if the cardiac output is 1 25 liters/min but the right atrial pressure is 0 mm Hg, this point lies on the fourth curve; this means that the heart is failing approximately 75 per cent despite the normal venous pressure.

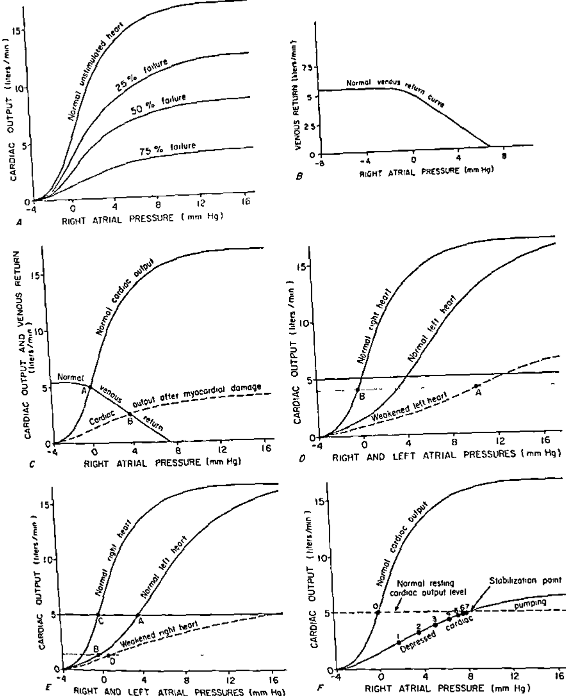


Fig 18-1. A Cardiac output curves for the normal heart and for hearts with 25 per cent, 50 per cent, and 75 per cent failure, respectively B A normal venous return curve C. Method of equating a venous return curve with a cardiac output curve, and the effect of myocardial damage on cardiac output and venous return. D Cardiac output curves for the normal right heart, the normal left heart, and a weakened left heart, illustrating the effect of a weakened left heart on cardiac output, right atrial pressure, and left atrial pressure E Cardiac output curves for the normal left heart, the normal right heart, and a weakened right heart, illustrating the effect of a weakened right heart on cardiac output and right and left atrial pressures F Cardiac output curves for a normal heart and for the same heart immediately after the pumping efficiency of the heart has been markedly decreased. This figure illustrates the increases in cardiac output and right atrial pressure on successive days after the acute depression of the heart.

It should also be noted that the failing heart can often pump a normal cardiac output provided the right atrial pressure is high enough. The third curve of Fig. 18-1B illustrates a heart that has lost 50 per cent of its pumping effectiveness but, still, when the right atrial pressure rises to approximately 2.4 mm Hg, the cardiac output becomes essentially normal. However, exercise and other cardiac stimulants fail to raise the cardiac output as much as usual because the heart, even under resting conditions, is already pumping blood almost as rapidly as it can. In other words, a greatly weakened heart, when primed sufficiently with inflowing venous blood, can often pump the same amount of blood per minute under resting conditions as can the normal heart, but the *cardiac reserve* is greatly diminished.

REGULATION OF CARDIAC OUTPUT AND VENOUS RETURN IN FAILURE

The amount of blood pumped by the heart each minute is not determined only by the ability of the heart to pump blood, for the rate at which blood returns to the heart from the veins is also a determining factor. In other words, cardiac output is determined by both (1) the effectiveness of the heart as a pump and (2) the tendency for blood to flow from the veins into the heart. The effectiveness of the heart as a pump can be quantitated by use of cardiac output curves as described above, while the tendency for blood to return from the veins can be depicted by "venous return curves" (Guyton, 1955 and 1956) (Fig. 18-1B). The important points of these curves may be described as follows.

Factors that Affect Venous Return. RIGHT ATRIAL PRESSURE. The curve of Fig 18-1B illustrates the effect on venous return of changing the right atrial pressure. When the right atrial pressure is less than 0 with respect to the atmosphere, the veins entering the thoracic cavity collapse, this prevents the negative pressures of the chest from sucking blood into the heart (Part 2). Therefore, the amount of blood that returns to the heart remains almost constant at all right atrial pressures lower than 0 mm Hg. On the other hand, when the right atrial pressure rises above 0, the pressure backs up into the peripheral veins, distending them and slowing down the flow of blood toward the heart. In the normal animal with normal vasomotor tone throughout its body, a rise of right atrial pressure to 7 mm Hg stops the flow of blood to the heart entirely (Guyton et al, 1954b). Obviously this decrease in venous return to zero makes the mean arterial pressure fall down to 7 mm Hg at the same time that the venous pressure is rising up to this value.

Application of the principles shown in Fig 18-1B to heart failure are obvious, for decreased pumping effectiveness of the heart normally increases the right atrial pressure, and this in turn depresses the venous return If the heart's pumping ability is only slightly impaired, excessive fall in venous return may be prevented by the compensatory effects of increasing vasomotor tone and increasing blood volume, which will be discussed later. But when the pumping effectiveness is decreased to a very great extent, each additional rise in right atrial pressure can no longer be compensated, and the venous return may fall disastrously, as much as 14 per cent for each mm Hg rise in right atrial pressure.

EFFECT OF BLOOD AND INTERSTITIAL FLUID VOLUMES ON VENOUS RETURN. Increasing the blood volume raises the blood pressure in each respective vessel throughout the circulation, and, as a result, the venous return correspondingly increases. An increase in interstitial fluid volume also increases the rate of venous return but in a slightly different way. The increased fluid in the interstitial spaces presses against the outside of the vessels, thereby increasing the blood pressure inside the vessels This pressure in turn promotes increased blood flow toward the heart In other words, an increase in either blood volume or interstitial fluid volume can compensate to a considerable extent for depressed cardiac pumping effectiveness. To present this idea in another way, increased blood or interstitial fluid volume increases the tendency for blood to return from the vascular system to the heart, and *even a weakened heart, when primed with increased quantities of inflowing blood, can often pump a normal cardiac output.*

EFFECT OF INCREASED VASOMOTOR TONE ON VENOUS RETURN AND CARDIAC OUTPUT. Increasing the vasomotor tone is another factor which will increase venous return and cardiac output When generalized increase in vasomotor tone occurs *throughout* the circulation, the tightening of each vessel against the enclosed blood increases the pressure, and this forces blood toward the right atrium at an increased rate of flow. One might expect generalized in-

crease in vasomotor tone always to increase the resistance to blood flow toward the heart However, this is not true for the following reason *When* a vessel constricts, it must displace its enclosed blood into some other vessel, but when all vessels attempt to constrict proportionately at the same time, no one vessel can constrict because each of them is trying to displace its blood into the others. The net result is simply an increase in the pressures throughout the circulation without any vasoconstriction. This is the result found experimentally when epinephrine is injected into an animal, and also occurs during generalized sympathetic stimulation Therefore, the amount of blood that returns to the heart from the veins is greatly increased by either epinephrine injection or sympathetic stimulation In this way, then, generalized increase in vasomotor tone, like increased blood volume, *often* compensates for depressed pumping *effectiveness* of the heart

Graphic Method for Analyzing the Equilibrium between Venous Return and Cardiac Output Figure 18-1C illustrates a graphic method by which one can analyze the effect of many different factors simultaneously on cardiac output and venous return In this graph, the two solid curves represent the effect of different levels of right atrial pressure on the normal cardiac output and the normal venous return respectively Note that increasing *the right atrial pressure increases the cardiac output but decreases the venous return* At the right atrial pressure, at which the two curves cross, the cardiac output and the venous return are exactly equal. At any right atrial pressure above this value, the venous return is less than the cardiac output, and at any right atrial pressure less than this value, the venous return is greater than the cardiac output Occasionally, some abnormality occurs which throws venous return and cardiac output temporarily out of equilibrium For instance, a sudden transfusion of blood into the right atrium instantaneously increases the right atrial pressure to a high value. As a result, the cardiac output becomes very great but the venous return very low, which means that the heart is pumping far more blood out of the right atrium than is returning to the [illegible] atrium [illegible] how[illegible] have [illegible] right atrial pressure will have fallen back to a low enough value that venous return once again equals cardiac output *Thus, the balance between cardiac output and venous return is always reestablished within a few heart beats*, and the crossing point of the cardiac output and venous return curves (point *A* on the graph) represents the stabilized levels of cardiac output, venous return, and right atrial pressure.

If any factor should change the ability of the heart to pump blood or should change the tendency for blood to return to the heart, then point A would no longer represent the actual operating conditions For instance, if the pumping effectiveness of the heart should be depressed from the solid curve to the lower dashed curve, then the new cardiac output curve and the venous return curve would cross at point B, the cardiac output now would be about one-half normal and the right atrial pressure would have risen approximately 4 mm Hg This graphical demonstration of the shift in operating conditions from point A to point B, therefore, represents a method for analyzing the effects on the circulation of depressing the pumping effectiveness of the heart from normal to about one-third normal Similar procedures may be used for depicting the effects of increased blood volume, increased peripheral resistance, sympathetic stimulation, and other factors, on the cardiac output, venous return, and right atrial pressure (Guyton, 1955 and 1956)

DYNAMICS OF ACUTE HEART FAILURE

More frequently than not both sides of the heart fail simultaneously, but occasionally one side of the heart fails by itself The present discussion will consider, first, the dynamics of one-sided failure, and then these will be synthesized into the over-all effects of combined failure

Dynamics of Acute Left-sided Failure. Acute failure of the left heart means depressed ability of the left ventricle to pump blood from the pulmonary veins into the aorta *As a consequence*, blood shifts out of the *systemic* circulation into the pulmonary *circulation*, damming up in the entire pulmonary vascular tree The pressures throughout the pulmonary system, especially in the veins, rise while those *in the* systemic circulation, including the *systemic veins*, fall slightly rather than rising

Figure 18-1D illustrates the dynamics of cardiac function in left-sided failure. The dashed curve is the cardiac *output curve* of a failing left heart while the sol[illegible] of the [illegible] [illegible] *output* It can be seen that the normal left heart pumps a cardiac output of 5 liters/min when the left atrial pressure is approximately +4 mm Hg, while the output of the *right* heart is *this* same amount when the right atrial

pressure is 0 mm Hg. When left heart function is acutely depressed, the damming of blood in the pulmonary vessels causes the pulmonary blood volume to increase as much as 100 per cent immediately (Lindsey et al.), which greatly increases the left atrial pressure. Simultaneously, the shift of blood out of the systemic circulation slightly decreases the right atrial pressure. Thus, in the figure, the left atrial pressure rises from 4 to 10 mm Hg (point *A*) while the right atrial pressure falls from 0 to −0.4 mm Hg (point *B*). The great rise in left atrial pressure allows even the weakened left heart to pump approximately 4 liters of blood per minute. Because of the decrease in right atrial pressure, the right ventricle also pumps this same quantity of blood. The dotted horizontal line, therefore, represents the new cardiac output level It is evident from this graph that depression of the ability of the left heart to pump blood greatly increases the pulmonary venous pressure and decreases slightly both the right atrial pressure and cardiac output.

The principal effect of acute left failure, then, may be mainly pulmonary congestion with only slight changes in other cardiovascular functions. However, if the damage to the left ventricle is considerably greater than that illustrated in Fig 18-1D, the cardiac output also may be greatly depressed, sometimes even down to shock levels, but this is always accompanied by extreme pulmonary congestion

Dynamics of Acute Right-sided Failure. When the right side of the heart fails rather than the left, blood is dammed in the systemic vessels, and an insufficient quantity of blood fills the pulmonary system. The quantity of blood in the lungs is diminished by as much as 50 per cent while that in the systemic circulation is correspondingly increased (Lindsey et al.). The main difference between left heart failure and right heart failure is caused by the difference in the capacities of the systemic and pulmonary circulations to store blood. *The venous pressure of the systemic circulation rises only one-tenth as much as that of the pulmonary circulation for each quantity of blood added* Consequently, a relatively small amount of blood shifting into the lungs can cause extreme symptoms of congestion while all the blood that can possibly shift from the lungs into the systemic circulation usually causes no perceptible peripheral congestion. As a result, in acute right failure, shift of blood from the lungs to the systemic circulation causes the right atrial pressure to rise only a very few mm Hg, almost never enough to cause significant signs of peripheral congestion immediately after the failure begins.

Acute right heart failure depresses cardiac output far more drastically than acute left heart failure for the following reason When the right heart fails, the quantity of blood that shifts from the lungs into the systemic circulation is too small to increase the right atrial pressure more than a few millimeters (Hg). This is not enough to compensate significantly for the depressed pumping effectiveness of the right heart. In contrast to this, in left heart failure, enough blood always shifts into the lungs to elevate the left atrial pressure significantly, and this can go a long way toward compensating for the weakness of the left heart.

The dynamics of right heart failure are illustrated in Fig. 18-1E which shows the normal cardiac output curve for the right heart, the normal cardiac output curve for the left heart, and a dashed curve representing the failing right heart. When the right heart fails, blood shifts out of the lungs depressing the left atrial pressure from point *A* to point *B*, and, at the same time, this blood shifts into the systemic circulation raising the right atrial pressure from point *C* to point *D* As a result, the normal cardiac output falls from that represented by the solid horizontal line to that represented by the dotted line through points *B* and *D*

The only clinically significant effect illustrated in this diagram is *the greatly depressed cardiac output,* for the changes in left and right atrial pressures are not sufficient to cause symptoms. Thus, acute right heart failure is characterized especially by low cardiac output but by almost no congestive symptoms

Combined Left- and Right-sided Acute Heart Failure. When both sides of the heart fail acutely at the same time, the heart is unable to pump blood satisfactorily either from the pulmonary veins into the aorta or from the systemic veins to the pulmonary artery One might suspect offhand that this would cause congestion in both the systemic circulation and in the lungs. However, this is not true because, *if the degree of failure in the two sides of the heart is exactly proportional, no blood shifts either from the pulmonary circulation into the systemic circulation or in the opposite direction.* However, cardiac

output is depressed directly in proportion to the degree of cardiac failure—the greater the degree of failure, the greater the depression in cardiac output. Therefore, the net effect of acute, simultaneous depression of both sides of the heart is principally a decrease in cardiac output and venous return but very few if any symptoms of either pulmonary or peripheral congestion. The venous pressures in both the pulmonary and systemic circulations rise slightly because of shift of blood from the arteries and blood reservoirs into the veins but not because of displacement of blood from one of the circulations to the other

FACTORS WHICH COMPENSATE FOR ACUTE FAILURE

Effect of Increased Sympathetic Activity Following Acute Failure. One of the most important immediate compensations for depressed pumping ability of the heart after acute failure *is an increase in the degree of sympathetic activity.* Several reflexes cause this increase, though exactly which is the most important is not completely known First, depressed pumping tendency by the heart tends to depress the arterial pressure, which elicits *the pressoreceptor reflex* and thereby increases the sympathetic tone Second, decreased flow of blood to the carotid and aortic chemoreceptors likewise initiates *sympathetic reflexes* Third, decreasing pressures in the pulmonary arterial tree and rising pressures in the great veins of the chest can at times elicit *sympathetic reflexes* Fourth, depression of blood flow to the brain in some instances initiates *sympathetic impulses* because of ischemia in the vasomotor center Regardless of which of these reflexes is most responsible, it is nevertheless a fact that, immediately after the heart has become weakened, the sympathetic nervous system becomes excessively active In experiments in which the functions of the sympathetic nervous system have been blocked, the animal always succumbs at a degree of cardiac depression far less than that which would be necessary to kill an animal with intact reflexes (Guyton et al., 1954a)

Increase in sympathetic stimulation helps to compensate for depressed cardiac pumping effectiveness in two ways: First, *sympathetic impulses directly stimulate the heart* and make those portions of the myocardium which have not been damaged more active than normal. Second, sympathetic stimulation *increases the venous return.* As explained earlier in this chapter, the generalized increase in vasomotor tone caused by sympathetic activity elevates the respective pressures in each segment of the circulation, and this accelerates blood flow toward the right atrium Thus, the heart is primed sufficiently to increase its output even though it is in a weakened condition

In summary, then, almost immediately after acute heart failure occurs, whether it be acute left-sided failure or acute right-sided failure, the falling cardiac output elicits vasomotor reflexes that can go a long way toward compensating for the weakness of the heart. Indeed, if the heart's pumping ability is depressed no more than 50 per cent, it can be expected that the person will experience nothing more than a momentary state of circulatory depression, because the increase in sympathetic tone can almost entirely compensate for this amount of weakness as long as the subject remains relatively inactive.

The Compensatory Effect of Fluid Retention in Cardiac Failure. In the foregoing discussion of the factors which affect venous return, it was pointed out that an increase in either blood or interstitial fluid volume can increase the venous return. Immediately after acute failure, both of these fluid volumes begin to increase for two reasons: First, the sympathetic reflexes which occur when cardiac output is depressed *are especially prone to constrict the renal vessels,* more so, indeed, than almost any other vessels in the body (Smith) This in turn depresses the urinary output of the kidneys, sometimes even to the extent of anuria. During the ensuing days, the blood volume and interstitial fluid volumes increase, resulting in increased return of blood to the heart. The heart becomes primed with progressively greater and greater quantities of blood until, despite its weakness, it may pump a normal cardiac output after several days of fluid retention.

The second factor which causes fluid retention in heart failure *is the stress mechanism* that causes the adrenocortical glands to secrete salt-retaining hormones, *aldosterone* in particular (Davis et al., 1956). Low cardiac output induces cellular stress through the entire body because of the resultant tissue is-

chemia. This in turn, by means not yet entirely understood, elicits rapid production of the adrenocortical hormones, and these then act on the kidneys to promote salt and water retention. This mechanism, therefore, in addition to the direct effect of low cardiac output on the kidney, *causes the body fluids to increase.*

The effects of fluid retention on cardiac output are illustrated graphically in Fig. 18-1F which shows, from top to bottom, the cardiac output curve of a normal heart and the cardiac output curve of a heart acutely depressed. The normal resting cardiac output is represented by point 0 on the normal curve but, immediately after failure begins, the cardiac output will have fallen to point 1 on the lower curve, and the right atrial pressure will have risen a few millimeters of mercury because of the damming of blood in the veins and also because of reflex vasomotor constriction. During the ensuing few days, retention of fluid causes progressively more and more return of blood to the heart and consequently a progressively rising right atrial pressure. On the second day, the right atrial pressure will have risen to point 2, on the third day, to point 3, and, on the fourth, fifth, sixth, and seventh days, to respectively higher pressures The cardiac output also will have been rising at the same time When sufficient fluid has been retained that the cardiac output has risen back to a normal value (at point 7), the vasomotor reflexes elicited by depressed cardiac output no longer remain active, this allows blood once again to flow through the kidneys at a normal rate. As a result, the anuria or oliguria disappears, though in the meantime the right atrial pressure will have risen to 8 mm Hg.

Thus, the retention of fluid acts as a slowly developing compensatory measure, increasing the cardiac output back toward normal when the heart has been weakened If the degree of failure is slight enough that the cardiac output can rise all the way back to normal, further retention of fluid by the kidneys ceases, and the patient becomes stabilized at this point with a permanently elevated right atrial pressure.

EFFECT OF FLUID RETENTION ON THE SYMPTOMS OF CONGESTION. Even though fluid retention may be beneficial to the cardiac output, it also aggravates the symptoms of pulmonary or peripheral congestion. In the case of primarily left-sided failure, the pressures in the lungs are already elevated, and the pulmonary congestive symptoms obviously are only compounded by the fluid retention. Congestive symptoms in the systemic circulation usually do not occur immediately after acute heart failure, whether it be left or right. However, in right or combined heart failure, the fluid retained during the days following the onset of failure gradually increases the pressures in all the systemic vessels, particularly in the veins, resulting in progressive peripheral venous congestion. Thus, as fluid retention progresses, so also do the peripheral congestive symptoms.

PERIPHERAL EDEMA RESULTING FROM HEART FAILURE. When the right heart begins to fail, whether this be right or combined heart failure, the immediate effect on capillary pressure is probably to decrease rather than to *increase it (Guyton et al, 1952).* The reason for this is that the damming up of blood backwards from the right atrium into the capillaries is more than compensated by the depressed flow of blood from the arteries into the capillaries. *Therefore, peripheral edema normally does not result immediately after an acute heart attack.* However, when the failure passes into the chronic state and is compensated by fluid retention, then the capillary *pressure begins to rise* for two reasons: First, as fluid is retained, it increases the venous blood volume resulting in progressively more and more damming of blood in the capillaries Second, fluid retention usually increases the cardiac output by increasing the venous inflow to the heart. As the output rises, the increasing flow of blood through the arteries to the capillaries also elevates the capillary pressure. Thus, even though the immediate effect after an acute heart attack is not to cause edema, nevertheless, as fluid is retained by the kidneys, the capillary pressure rises progressively and most of the retained fluid then leaks into the tissues, resulting in progressive edema

DYNAMICS OF DECOMPENSATION AND ITS RELATION TO CARDIAC OUTPUT

The term "decompensation," like "heart failure," is beclouded by many different definitions The present discussion will consider decompensation as "that state in which the symptoms of pulmonary and peripheral con-

gestion are progressively increasing and the cardiac output may be falling " Eventually all of these factors progress to the point at which the patient must die unless some treatment is instituted to reverse the progression of symptoms

Figure 18-2A illustrates the dynamics of decompensated heart failure The cardiac output curve of this figure is that of a heart in which pumping ability has been decreased to only 15 to 20 per cent of normal. Immediately after the heart fails, the cardiac output falls approximately to point 1 on the curve At this point, the right atrial pressure is only 4 mm Hg, which is not greatly above normal The low cardiac output, however, initiates fluid retention, as was previously explained. Each day more and more fluid is retained but, because of the tremendous depression of the heart's ability to pump blood, even on the third, fourth, fifth, and sixth days, the cardiac output still will not have risen up to the normal level represented by the dashed line. Consequently, the vasomotor reflexes initiated by low cardiac output remain active, and the output of urine by the kidneys never rises back to normal Fluid continues to be retained even when the cardiac output has risen to as high a volume as the heart can possibly pump, and, in the ensuing days, the seventh, eighth, ninth, and tenth days, still more and more fluid is retained causing

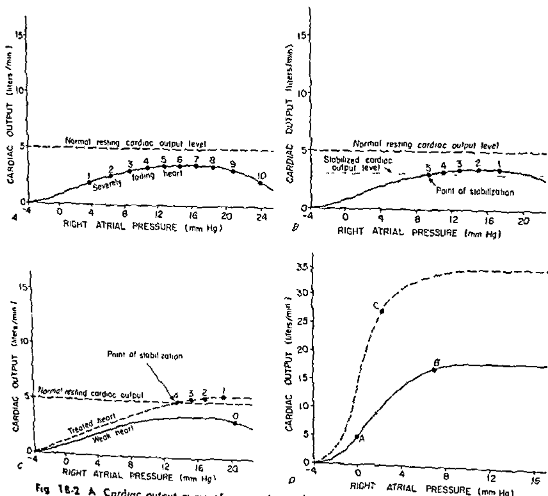


Fig 18-2 A Cardiac output curve of a greatly weakened heart showing the changes in right atrial pressure and cardiac output on successive days after the heart has become acutely weakened. B Compensation of a previously decompensated heart by control of the fluid intake and fluid output (explained in text) C Compensation of a previously decompensated heart by strengthening the myocardium (explained in text) D. Cardiac output curves of a normal heart (solid line) and of a hypertrophied heart (dashed line), showing the effects on the dynamics of cardiac output and right atrial pressure of the greatly enhanced venous return which occurs in high cardiac output failure

more and more edema, more and more peripheral congestion, and eventually the death of the patient.

One of the effects of decompensation is *a terminal decrease in cardiac output.* The exact cause of this has not been completely determined, but it may result from several different factors. First, many physiologists and clinicians have claimed that the main cause might be distention of the heart beyond its normal limits of operation. The effect of this on the cardiac output curve is illustrated in Fig. 18-2A by the decline in the curve at the very high right atrial pressure levels rather than a continuing rise. However, in most experiments on animals this decline is not very extensive. Therefore, it is probable that the final decrease in cardiac output in the decompensated patient is not caused principally by excessive distention of the heart but by other factors. For instance, *edema or ischemia of the myocardium caused by the heart failure could make the heart become even weaker,* thus resulting in more extensive failure with the effect progressing into a vicious cycle of deterioration. Regardless of the exact cause, in the last stages of decompensation the heart goes into a declining phase of function which seems the result of a vicious cycle, the heart getting weaker and this weakness causing still further weakness of the heart until death supervenes

TREATMENT OF DECOMPENSATION

If decompensation has not reached the stage of a vicious cycle of cardiac deterioration, it can often be successfully treated by controlling the patient's fluid balance or by improving the pumping ability of his heart

Figure 18-2B illustrates the effects of treating a decompensated patient by controlling his fluid balance. The usual rate of cardiac output required for the kidneys to maintain normal fluid balance is about 5 liters/min. This level of output is indicated by the dashed line in Fig. 18-2B However, when the patient is placed on a low salt-and-water intake or given a diuretic, the level of cardiac output for maintenance of normal fluid balance might be reduced to as low as 3 liters/min.

In Fig. 18-2B, assume that an untreated patient is in a state of decompensation and that he has reached point 1 on the curve. Then therapy is instituted, so that the cardiac output level required for maintenance of fluid balance is reduced from 5 to 3 liters/min. This is 0 5 liter/min less than the patient's actual cardiac output. Therefore, the fluid output becomes greater than the fluid intake, and the body fluids begin to diminish. The right atrial pressure falls the first day from point 1 to point 2, the second day to point 3, the third day to point 4, and eventually to point 5. In this way the right atrial pressure progressively falls until the cardiac output becomes exactly sufficient to maintain a normal fluid balance. This point of stabilization is point 5 on the graph. The progressive symptoms of decompensation then will have been abated, and the patient will not go on to the vicious cycle of cardiac deterioration.

Treatment of Decompensation by Improvement of Cardiac Function. Figure 18-2C illustrates by the lower cardiac output curve a state of decompensation. Before treatment, the patient has reached point 0 on the curve. Then the patient is treated either by rest therapy or by administration of a drug such as digitalis that increases the effectiveness of cardiac pumping. The result is an increase in the cardiac output curve from the lower solid curve to the upper dashed curve The increased pumping effectiveness immediately lowers the right atrial pressure from point 0 to point 1 and also increases the cardiac output to a rate above the 5 liters/min needed by the kidneys to maintain normal fluid balance. As a result, diuresis occurs and the right atrial pressure falls by the second day to point 2, by the third day to point 3, and by the fourth day to point 4. At this time the cardiac output will have fallen back to the normal value of 5 liters/min at which level the balance between fluid intake and output is reestablished. The patient stabilizes at this point. Thus, the progressive symptoms of decompensation are abated, and the disease does not reach the stage of final cardiac deterioration

In summary, most of the effects of decompensation are initiated by failure of the heart to pump quantities of blood adequate to permit the kidneys to maintain normal fluid balance As a result, progressive fluid retention causes the right atrial pressure to rise, and the symptoms of congestion and edema to increase In the late stages of decompensation the edema, prolonged ischemia (and undoubtedly other factors) cause the pumping ability of the heart to begin to diminish, eventually resulting in a vicious cycle of cardiac deterioration The condition can usually be treated by measures that promote reestablishment of fluid balance. *The two most effective procedures are* (1) treatment of the patient so that the pumping ability of his heart is

increased (by either rest or administration of a glucoside) and (2) salt restriction in the diet, combined with administration of diuretics.

FORWARD VERSUS BACKWARD THEORY OF FAILURE

The terms *forward* and *backward failure* are mentioned in this discussion only for the purpose of explaining their meaning and not to perpetuate their usage in discussions of cardiac failure *Actually, when a heart fails to pump adequately, it both fails to pump blood forward and at the same time dams blood up backwards* Therefore, both effects always occur together, and use of the terms "forward" and "backward" can at times be extremely confusing The meaning of the term "forward failure" is that the symptoms are mainly attributable to diminished cardiac output which, by connotation, is considered to be the "forward" function of the heart. The term "backward failure" means that the symptoms are mainly attributable to the damming of blood behind the heart rather than to diminished output Thus, low cardiac output failure is the same as forward failure, and the symptoms attributable to this are mainly those of ischemia of the different organs of the body For instance, cardiac shock is forward failure On the other hand, backward failure embraces both pulmonary congestion and peripheral congestion. A far better and more physiological description of the different clinical types of failure would be simply the following three basic categories: (1) low output failure, (2) failure with pulmonary congestion, and (3) failure with peripheral congestion Each of these types of failure can occur almost entirely independently of the other two, any two may occur together, or they all may occur simultaneously, depending on which portions of the heart are failing, the degree of failure, and whether or not the failure is acute or chronic.

DYNAMICS OF HIGH CARDIAC OUTPUT FAILURE

High cardiac output failure does not necessarily mean that the heart itself is in a weakened state, but it means instead that the heart is not able to pump all of the blood that is flowing into it from the blood vessels. Indeed, the heart may be completely normal but the amount of blood flowing into it may be so great that even a normal heart is unable to pump it all. Physiologically, this circulatory state should not be considered to be failure of the heart, but some other term, such as *cardiac overloading* should be used to describe it.

The two principal causes of high cardiac output failure are (1) *increased blood volume*, such as occurs immediately after a massive tranfusion or following administration of excess adrenocortical hormones, and (2) *greatly diminished peripheral resistance* allowing very rapid blood flow through the systemic circulation. This occurs in beriberi heart disease, sometimes during excessive exercise, and often in arteriovenous fistulas. In all these conditions, so much blood flows into the right atrium that the heart is *totally unable to cope with it* Much of the blood, therefore, is dammed up in the veins causing symptoms of congestion which simulate those of true heart failure

The dynamics of high cardiac output failure are illustrated in Fig 18-2D. The solid cardiac output curve is that of a normal unstimulated heart, and the normal cardiac output is represented by point *A* If a heart suddenly becomes overloaded by excessive blood flow into the right atrium, the right atrial pressure might rise to 7 mm Hg causing a corresponding increase in cardiac output to 17 liters/min, which is represented by point *B*. The cardiac output remains high as long as the load of blood returning to the heart remains elevated If this state lasts for weeks or more, the excessive work load on the heart causes it to hypertrophy, progressively increasing the ability of the heart to pump blood until its cardiac output curve becomes the one represented by the dashed curve. This increased pumping ability of the heart increases the cardiac output another 10 liters/min from point *B* up to point C, and it lowers the right atrial pressure almost back to normal because the heart can now cope with its excessive load much more effectively than it could immediately after the extra load had first been applied

It is evident then that high cardiac output failure is not failure of the heart at all, but instead is a condition resulting from increased tendency for blood to return from the vessels to the heart. That is, *it is an abnormality of the extracardiac portion of the circulatory system rather than of the heart.*

Metabolic factors of heart failure

PETER TALSO

In the classical considerations of congestive heart failure, the physician has tended to focus his attention primarily on the dynamic aspects, namely, those having to do with the altered dynamics of the heart, with changes in the venous pressure, and with alterations in the hemodynamics of the kidney. Later, however, it was recognized that certain manifestations of congestive failure may be related to metabolic disorders that either develop as a result of failure or may be their prime cause. The present discussion will be limited to a consideration of metabolic changes in the body as a whole while alterations in the intimate metabolism of cardiac muscle will not be considered.

The metabolic aspects of congestive heart failure will be considered in the following order: (1) oxygen consumption or metabolic rate, (2) water metabolism, (3) sodium and chloride metabolism, (4) potassium and nitrogen metabolism, and (5) fat metabolism

METABOLIC RATE

The oxygen consumption of patients in congestive failure has been extensively studied by many workers Perhaps the earliest observations of this kind were those of Peabody and his group, who observed that the "basal oxygen consumption" of patients in congestive failure was considerably higher than that found in normal individuals. Following these observations, an increased oxygen consumption in heart failure has been recorded by many observers More recently, studies of oxygen consumption have been correlated with measurements of protein-bound iodine, of I^{131} uptake, and of radioiodine conversion ratio in patients with heart failure. From studies of this sort, it has been possible to deduce that *the increased metabolic rate observed in congestive heart failure is nonthyroidal in origin and that it is probably due to the increased work demand placed upon the organism as a whole by respiratory distress, by the increased size of the heart, and, perhaps, by other factors such as emotional tension* In some patients with hypertension or rheumatic valvular disease, the basal oxygen consumption has been reported by some to be increased in the absence of frank congestive failure. The mechanism by which this occurs has not been elucidated. The significance of the increased metabolic rate observed in congestive failure and its relationship to the cardiac patient will be discussed below (nitrogen and potassium metabolism)

An increase in oxygen consumption in the presence of a disease state in which *hypoxia* plays a major role seems paradoxical; however, when it is considered that the hypoxia may be localized and limited to a single organ or organ system, it becomes apparent that the two conditions are not mutually exclusive

Another important aspect of respiratory metabolism in congestive failure is the exchange of carbon dioxide In the average patient in failure, changes in carbon dioxide exchange may be minimal. If, however, pulmonary function is compromised by pneumonia, pulmonary infarction, or massive pleural effusion, the removal of carbon dioxide may be interfered with If the resultant retention of carbon dioxide is of sufficient mag-

nitude, serum carbonic acid and serum bicarbonate concentrations rise resulting in *respiratory acidosis* (Fig 18-3A) The narcosis of the medullary respiratory centers accompanying respiratory acidosis and the dangers attendant on oxygen administration under such circumstances are well known and need no further comment.

Water Metabolism. One of the prominent clinical findings in patients with congestive heart failure is the presence of *dependent edema, ascites,* and often *pleural effusion* These findings are directly related to alterations in water metabolism Numerous studies of water metabolism in these patients have been reported; however, the precise mechanism by which water metabolism is altered in this disease state is still unknown The early studies of Starling suggested that edema fluid was retained through a mechanism of transudation and that this was due to increased capillary pressure resulting from backward *failure.* Studies performed in carefully controlled clinical situations have demonstrated that this explanation is not tenable in every instance As a result, other explanations have been sought. Studies of urine extracts have demonstrated that *the urine of patients with congestive heart failure contains an increased quantity of an antidiuretic substance somewhat similar to that found in extracts of the posterior pituitary gland* (Bercu et al.). Other studies have presented evidence that, in heart failure, the increased amounts of antidiuretic substance do not result from decreased destruction of this material but rather from increased production (White et al). This finding would suggest that in part the altered water metabolism of congestive heart failure is related to an increased formation of posterior pituitary antidiuretic substance The stimulus to the production of an increased quantity of antidiuretic substance, however, has not been accurately identified. In the classic work of Verney, it was demonstrated that an increase in the osmolarity of the blood entering the area of the pituitary stalk, the posterior pituitary, and the supraoptical hypophyseal nuclei would produce an antidiuretic response and, therefore, presumably an increased secretion of antidiuretic hormone. It has been proposed that, early in the course of congestive failure, there is a phase of increased intravascular osmolarity resulting from a decreased intravascular volume This would provide the necessary stimulus for an increased secretion of

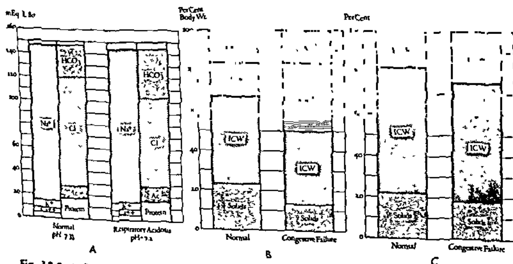


Fig. 18-3 A Respiratory acidosis Note that the principal changes in serum electrolytes consist of an increase in carbonic acid and in bicarbonate with a decrease in serum chloride and in pH. B. Changes in body composition in congestive *failure Left* average percentage composition of a normal individual in health. Right average percentage *body composition* in congestive heart failure with *edema* C The percentage composition of solids, extracellular water (ECW) and intracellular water (ICW) in fresh, fat-free muscle samples obtained from normal persons and patients with edema due to congestive heart failure *Note that* the changes in these components parallel the changes in total body composition (B).

posterior pituitary antidiuretic hormone. The ultimate significance of the presence of such antidiuretic substances in the urine of patients with failure, together with the possible relationship of this fact to the pathogenesis of heart failure, remains to be elucidated.

In the recent studies of Laragh et al., edema was produced in dogs despite the fact that the animals had been rendered free of functioning posterior pituitary tissue. This would suggest that some factors, in addition to the posterior pituitary antidiuretic hormone, play a role in the retention of water in congestive heart failure or that antidiuretic hormone can be elaborated by other areas of the brain.

In addition to an increased quantity of antidiuretic hormone, several workers have demonstrated increased amounts of *adrenocortical substances in the urine* of patients with congestive heart failure (Deming et al.; Singer et al.). It has been proposed that the decreased volume of intravascular fluid associated with the hyperosmolarity previously mentioned provides a stimulus to the formation of increased adrenocortical hormones In addition, the stress of acute congestive failure undoubtedly contributes an additional stimulus to this mechanism. Whether the presence of increased adrenal hormones in the urine of patients in congestive heart failure represents a prime cause of the symptoms of congestive heart failure or whether it reflects still another concomitant manifestation of congestive heart failure is unknown. Certainly, these substances play a role in the altered electrolyte metabolism that is seen in heart failure, and, therefore, are undoubtedly secondarily related to the altered water metabolism.

Another mechanism which may contribute to the edema of congestive heart failure is *glomerulotubular imbalance*, as proposed by Mokotoff et al. According to this mechanism, glomerular filtration is decreased in heart failure while tubular reabsorptive capacity remains intact. As a result, water and sodium are retained. Such an explanation becomes untenable when it is observed that patients with heart failure may become edema-free despite the fact that the glomerular filtration rate remains at a low level. If, on the other hand, the decreased glomerular filtration rate is regarded as an incidental finding in heart failure and one postulates *an increased tubular reabsorptive capacity for sodium and water*, then by definition *glomerulotubular imbalance* may play an important role in the accumulation of edema fluid in heart failure. Unfortunately, the critical measurements of these discrete renal functions cannot be adequately performed with currently available techniques. The alterations in the discrete renal functions of sodium and water excretion described by Newman may play a significant role in the altered water metabolism of heart failure.

Numerous investigators have studied the total quantity of body water in patients in congestive heart failure while others have studied individual tissues for their water content. Studies of total body water have been carried out with the use of various dilution techniques, utilizing tritium- or deuterium-labeled water, antipyrine, or one of the antipyrine derivatives. Although some controversy persists with regard to the accuracy with which these substances measure the total body water individually, most investigators have agreed that *in congestive heart failure the estimated total body water is increased*. However, this increase is often not proportional to the amount of peripheral edema that is observed clinically. This discrepancy between the degree of clinically estimated edema and the measured quantity of water requires an additional explanation

It has been suggested that the relatively small increase in total body water as measured by these various techniques compared with the marked amount of edema sometimes observed clinically, results from *a marked increase in extracellular water* accompanied by a loss of intracellular water. Such an explanation requires an alteration in water distribution associated with a loss of tissue solids (Fig. 18-3B) Direct determinations on specimens of skeletal muscle obtained from edematous areas in patients with congestive heart failure lend credence to this explanation (Fig. 18-3C). The relationship of water metabolism to changes in tissue solids will be discussed further under protein metabolism With appropriate therapy, the total water content of patients with congestive failure promptly returns to normal.

Sodium Chloride. The recognition of the possible relationship of *sodium* and *chloride* to the manifestations of heart failure dates

back to antiquity Only in more recent times, however, have the independent mechanisms by which these ions are metabolized been recognized. In the average American diet, the intake of sodium averages from 100 to 175 milliequivalents daily Over the world as a whole, this value varies over a much wider range, depending upon the availability of salt, eating habits, and culture. Under normal circumstances, this amount of sodium is excreted each day via the skin, in the feces, and in the urine. In the presence of congestive heart failure the capacity of each of these avenues of sodium excretion becomes markedly diminished, most important, however, appears to be *the inability of the kidney to excrete sodium* In some patients with congestive failure, the amount of sodium recovered from the urine in a 24-hr period may approach zero, *even in the* presence of a considerable intake *of this ion* In this regard, studies on patients who have heart disease without edema have revealed that an increase in exchangeable sodium and in extracellular fluid volume occurs in these patients before a decrease in the ability of the kidney to excrete sodium is detectable (Hollander and Chobanian) The ultimate *mechanism* or mechanisms by which renal *sodium retention develops is unknown.* The possible role of *adrenocortical steroids in* the genesis of *edema in heart failure* has already been mentioned in the section on water metabolism. The *influence* of the adrenal steroids on renal tubular sodium reabsorption is well known

More recently, *interest* has been focused on *aldosterone* as the cause *of sodium retention* in this situation Bioassay studies of urine from patients with congestive heart failure have demonstrated that tremendous *quantities of this* substance may be present (Luetscher and Johnson). Such observations suggest that increased aldosterone production *may play a* role in the retention of sodium It is of interest that patients with *primary hyperaldosteronism do not* manifest peripheral edema, but present all *of the* other manifestations of increased aldosterone levels which are absent in congestive failure This problem has been reviewed by Johnson and Conn.

Measurements of exchangeable sodium[1] on patients with edema due to congestive heart failure have been carried out by several investigators These studies have demonstrated that the content of *exchangeable sodium* is significantly *increased* in all patients with congestive heart failure. Further, the increase in exchangeable sodium is disproportionately greater than is the increase in total body water. This can be explained in part by a marked increase in extracellular water, which has a high concentration of sodium, accompanied by a decrease in intracellular water, which is low in sodium or sodium-free (Fig. 18-3B). However, *the increase in exchangeable sodium* is large enough to suggest that other sodium stores are probably involved as well. Such potential stores include connective tissue, cartilage, and bone. It is of interest that the increase in the value for exchangeable *sodium* is often increased prior to the appearance of clinical edema and frequently remains elevated *for long intervals* after clinical edema has disappeared.

One other aspect of *sodium metabolism* in congestive heart failure which deserves consideration is the problem of *hyponatremia* In general, a serum sodium concentration of 135 *mEq/liter* is regarded as representing the lower limit of normal. Serum sodium concentrations lower than this are occasionally *observed in patients with* heart failure (Fig 18-4A). This finding usually *reflects a redistribution of sodium* in the presence of a total body excess of the ion and does not represent a deficiency syndrome.

The *chloride ion*, like the sodium ion, is predominantly extracellular, although it does occur *intracellularly* in certain tissues, such as the red blood cells, the gastric mucosa, and the testicle. In congestive failure, the body chloride increases in proportion to the extracellular fluid. Of greater importance, however, is the role that the chloride ion plays in the acid-base *metabolism* in congestive heart *failure In* uncomplicated and untreated congestive *failure*, the serum chloride concentration *remains* normal *despite* an increase in the total body chloride content *Following* the ad-

[1] Exchangeable sodium represents that portion of the body's total sodium stores which reaches equilibrium rapidly *following* injection of radioactive sodium Studies *indicate* that approximately two-thirds of the body's total *sodium* is exchangeable

posterior pituitary antidiuretic hormone. The ultimate significance of the presence of such antidiuretic substances in the urine of patients with failure, together with the possible relationship of this fact to the pathogenesis of heart failure, remains to be elucidated.

In the recent studies of Laragh et al., edema was produced in dogs despite the fact that the animals had been rendered free of functioning posterior pituitary tissue This would suggest that some factors, in addition to the posterior pituitary antidiuretic hormone, play a role in the retention of water in congestive heart failure or that antidiuretic hormone can be elaborated by other areas of the brain.

In addition to an increased quantity of antidiuretic hormone, several workers have demonstrated increased amounts of *adrenocortical substances* in the urine of patients with congestive heart failure (Deming et al.; Singer et al.). It has been proposed that the decreased volume of intravascular fluid associated with the hyperosmolarity previously mentioned provides a stimulus to the formation of increased adrenocortical hormones. In addition, the stress of acute congestive failure undoubtedly contributes an additional stimulus to this mechanism. Whether the presence of increased adrenal hormones in the urine of patients in congestive heart failure represents a prime cause of the symptoms of congestive heart failure or whether it reflects still another concomitant manifestation of congestive heart failure is unknown. Certainly, these substances play a role in the altered electrolyte metabolism that is seen in heart failure, and, therefore, are undoubtedly secondarily related to the altered water metabolism

Another mechanism which may contribute to the edema of congestive heart failure is *glomerulotubular imbalance*, as proposed by Mokotoff et al. According to this mechanism, glomerular filtration is decreased in heart failure while tubular reabsorptive capacity remains intact. As a result, water and sodium are retained. Such an explanation becomes untenable when it is observed that patients with heart failure may become edema-free despite the fact that the glomerular filtration rate remains at a low level If, on the other hand, the decreased glomerular filtration rate is regarded as an incidental finding in heart failure and one postulates *an increased tubular reabsorptive capacity for sodium and water*, then by definition glomerulotubular imbalance may play an important role in the accumulation of edema fluid in heart failure Unfortunately, the critical measurements of these discrete renal functions cannot be adequately performed with currently available techniques. The alterations in the discrete renal functions of sodium and water excretion described by Newman may play a significant role in the altered water metabolism of heart failure.

Numerous investigators have studied the total quantity of body water in patients in congestive heart failure while others have studied individual tissues for their water content. Studies of total body water have been carried out with the use of various dilution techniques, utilizing tritium- or deuterium-labeled water, antipyrine, or one of the antipyrine derivatives. Although some controversy persists with regard to the accuracy with which these substances measure the total body water individually, most investigators have agreed that *in congestive heart failure the estimated total body water is increased*. However, this increase is often not proportional to the amount of peripheral edema that is observed clinically. This discrepancy between the degree of clinically estimated edema and the measured quantity of water requires an additional explanation.

It has been suggested that the relatively small increase in total body water as measured by these various techniques compared with the marked amount of edema sometimes observed clinically, results from *a marked increase in extracellular water* accompanied by a loss of intracellular water. Such an explanation requires an alteration in water distribution associated with a loss of tissue solids (Fig. 18-3B). Direct determinations on specimens of skeletal muscle obtained from edematous areas in patients with congestive heart failure lend credence to this explanation (Fig. 18-3C). The relationship of water metabolism to changes in tissue solids will be discussed further under protein metabolism With appropriate therapy, the total water content of patients with congestive failure promptly returns to normal.

Sodium Chloride. The recognition of the possible relationship of *sodium* and *chloride* to the manifestations of heart failure dates

ing from congestive failure have demonstrated a cumulative balance of potassium which may be positive, negative, or zero Similarly, serial studies of exchangeable potassium in patients recovering from heart failure have demonstrated that, in some instances, the value for exchangeable potassium may increase whereas in others this value may diminish. It is of interest that patients in whom the value for exchangeable potassium decreased progressively despite therapy succumbed to congestive failure, patients in whom the value for exchangeable potassium increased, recovered These observations are of significance when interpreted in relationship to the alterations in protein metabolism Several investigators have demonstrated that during recovery from congestive heart failure a significant amount of nitrogen is retained. This positive nitrogen balance reflects a restoration of tissue protein stores In addition, it is of interest that, in samples of skeletal muscle obtained in patients during and following recovery from congestive failure, the ratio of potassium to nitrogen remains remarkably constant. This would suggest that, in patients with congestive heart failure who fail to achieve a positive potassium balance, there is a concomitant failure to achieve a positive nitrogen balance

In seeking an explanation for these alterations …

…sultant inadequate dietary intake may be a contributing factor. The increased metabolic rate previously referred to, increases the rate of tissue breakdown and increases the requirement for nutrient materials Superimposed infections, such as pneumonia or genitourinary infections, further increase the requirements and contribute to the negative nitrogen balance Congestive changes in the liver may interfere with liver function and limit the rate of synthesis of protein materials In addition, patients with congestive failure are forced to lead inactive sedentary lives and, as a result, skeletal muscle atrophies and is replaced by fat Finally, the stress of congestive failure with its concomitant discharge of adrenocortical substances provides an additional set of factors which contribute to tissue breakdown during the course of congestive heart failure.

The significance of a loss of body tissue in congestive heart failure has already been alluded to in the section on water metabolism. Recent studies of body composition in cachectic patients with congestive heart failure have demonstrated that, in these patients, there is loss of muscular tissue out of proportion to the loss of body fat (Fig. 18-3B). This situation is similar to the changes in body composition seen in patients with "wasting diseases" It would appear that, in congestive failure, the changes in body composition are similar to those associated with placing a fat man in a lean man's body In other words, cardiac cachexia is characterized by a marked loss of lean tissue, and an increase in relative body water and body fat content.

Fat. Many patients with congestive failure are obese This is particularly true in the middle-aged and elderly patient population The role of obesity in contributing to the pathogenesis of congestive failure is widely recognized in that excess fat increases the work demands upon the heart Unfortunately, accurate measurements of body fat content have not been carried out in patients with heart failure and the changes in body fat stores which may result from chronic heart failure or recurrent heart failure are inadequately understood despite the fact that the marked cachexia of chronic heart disease has long been recognized Most currently available methods for estimating body fat assume a normal body water content and, therefore, cannot be utilized in edematous patients. Other methods utilizing measurements of skin-fold thickness or x-ray diffraction techniques have not been standardized in edematous patients and are not applicable. Newer techniques for estimating body fat in the presence of congestive failure are currently being developed and, as they are applied, medical knowledge of the changes in body fat and lean-body mass will provide a more adequate description of the changes in body composition seen in congestive heart failure.

In summary, the metabolic aspects of congestive heart failure include alterations in the metabolism of water, sodium, chloride, potassium, and nitrogen. Total body water may be increased only slightly over the normal but, because of altered relationships between intracellular and extracellular phases, even small

ministration of *ammonium chloride* as a diuretic, the serum chloride concentration will rise in varying degrees depending upon the size of the dose, the amount of absorption, and the ability of the kidney to handle the increased chloride load. The increase in serum chloride concentration leads to a *hyperchloremic acidosis* of varying degrees of severity (Fig. 18-4B). If the hyperchloremia is moderate in degree, it has a transient diuretic effect in that, for 24 to 36 hr following the institution of therapy with ammonium chloride, a diuresis of water and sodium generally occurs. After 36 hours of continuous therapy, the ammonium-producing mechanism of the renal tubules comes into play and the diuresis of water and sodium is discontinued. In patients with extensive renal damage, the ability of the renal tubules to produce ammonium ion may be sufficiently diminished so that the excess load of chloride ion continues to be excreted in association with sodium ions. Under these circumstances, the chloride acidosis may become progressively more severe and can occasionally lead to death. In some patients with severe congestive failure, the sodium-retaining mechanism of the renal tubules may be so marked that the administration of ammonium chloride may not produce a sodium diuresis but instead may result in a significant renal loss of potassium. Generally, however, this is not manifested by a decreased serum potassium concentration. In acidosis, *hyperkalemia*, rather than hypokalemia, is the rule.

Another aspect of chloride metabolism associated with the therapy of congestive failure is the *hypochloremic alkalosis* which may follow the administration of *mercurial diuretics* (Fig. 18-4C). Since the organic mercurial compounds tend to promote a chloruresis out of proportion to the accompanying diuresis of sodium, the serum chloride concentration falls and this is accompanied by an increase in serum bicarbonate concentration and in serum pH. Frequently, the serum potassium concentration is also decreased under these circumstances and this hypokalemia may be manifested by muscular weakness and symptoms of digitalis intoxication. As a rule, when the serum chloride concentration falls to 85 mEq/liter or less, further administration of mercurials fails to produce a water diuresis, but the loss of chloride continues and the progressively more severe hypochloremic alkalosis may lead to coma and occasionally death.

Potassium and Nitrogen Metabolism. The importance of the potassium ion in relationship to cardiac function has been recognized for many years. However, the total metabolism of potassium by the patient in congestive heart failure was not investigated until much later. Metabolic balance studies in patients recover-

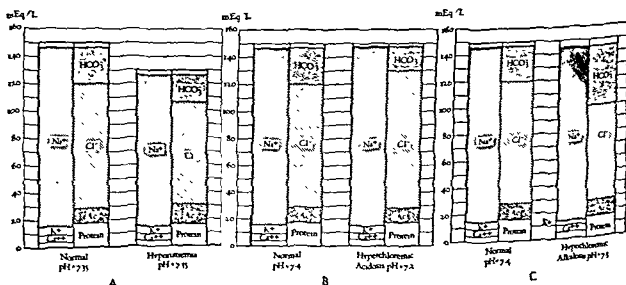


Fig. 18-4. A. Changes in serum electrolytes seen with hyponatremia in congestive heart failure. B. Hyperchloremic acidosis. Changes in serum electrolyte concentrations which may result from the ingestion of ammonium chloride, cation exchange resins, or carbonic anhydrase inhibitors. C. Hypochloremic alkalosis. Changes in serum electrolyte concentrations which may follow the administration of mercurial diuretics.

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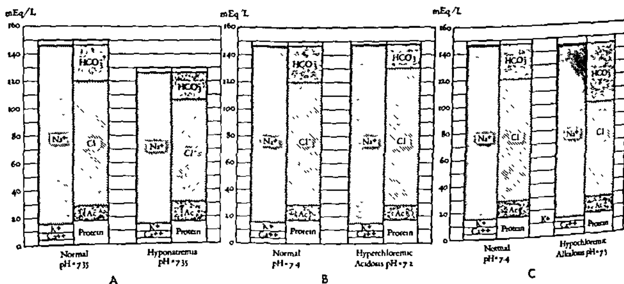


Fig. 18-4. A Changes in serum electrolytes seen with hyponatremia in congestive heart failure B. Hyperchloremic acidosis Changes in serum electrolyte concentrations which may result from the ingestion of ammonium chloride, cation exchange resins, or carbonic anhydrase inhibitors C. Hypochloremic alkalosis. Changes in serum electrolyte concentrations which may follow the administration of mercurial diuretics

4

Extracardiac factors of heart failure

PETER TALSO

Heart disease by its very definition presupposes an abnormal condition involving the structures of the heart *as an organ*. *In many* instances the heart itself may be structurally and functionally normal but, because of the operation of factors outside of the heart, symptoms and manifestations of heart disease become evident. In general, such extracardiac factors interfere with the integrity of the circulation by placing increased demands upon the heart. In other instances, however, a systemic disease process may influence the heart incidentally and occasionally the cardiac manifestations may be most prominent.

In the present discussion, extracardiac factors will be considered in the following categories:

1. Infections
2. Anemias
3. Endocrine factors
   - *a* Hyperthyroidism
   - *b* Hypothyroidism
   - *c* Adrenal factors
   - *d* Pituitary factors
4. Nutritional factors
   - *a* Beriberi
   - b Cirrhosis
   - c Obesity
5. Pregnancy
6. Paget's disease of bone
7. Muscular dystrophies

This list is not intended to be exhaustive, but serves to *emphasize* the wide variety of factors which may be operative in producing manifestations of cardiac disease in a given patient. Their importance lies in the fact that many of them can be corrected and thus the prospects for recovery are vastly improved.

INFECTIONS

The relationship of specific infectious processes, such as rheumatic fever, syphilis, and certain viral diseases, to diseases of the heart are well known and have been adequately documented in other sections of this text (see Part 8). In addition to these, however, infections generally may have an effect upon the heart. It is well known that, as the body temperature rises, the rate of metabolism increases approximately 13 per cent for each degree of fever above normal on the centigrade scale. With this, cardiac output increases proportionately through increases of heart rate and stroke volume. In individuals with normal hearts, this increase in cardiac work is readily tolerated and symptoms referable to the heart are minimal. If, however, the heart's integrity has already been compromised by the presence of such conditions as mitral stenosis, hypertension, or atherosclerotic heart disease, then *the increased demands occasioned by the fever may precipitate congestive heart failure*. It is important for the clinician to realize that minor infections, which are of no consequence to normal persons, may be of sufficient importance in persons with heart disease to initiate serious and even fatal congestive heart failure. In elderly persons, infections and the accompanying fever may result in *atrial fibrillation*, which in turn can lead to congestive failure. As a result, every patient undergoing an episode of congestive heart failure should be studied carefully in order to eliminate the possibility of a secondary infection as the precipitating cause.

increments of water may produce spectacular clinical edema. Body sodium stores are increased, and this increase is much greater proportionately than is the increase in body water. Body chloride is increased in proportion to the increase in extracellular water. Changes in serum chloride concentration may be induced by conventional therapeutic procedures and may occasionally play a major role in determining the outcome of an individual case Body potassium and nitrogen stores are depleted and this loss of tissue appears to influence the distribution of water. The capacity of the patient to replenish these tissue stores may determine to a significant degree the patient's recovery.

defects, e g., rheumatic, atherosclerotic, or *hypertensive conditions*, are present as underlying causative factors.

Therapy of thyrotoxicosis has been greatly simplified by the availability of I^{131}, although in patients of childbearing age, antithyroid drugs such as propylthiouracil and methylthiouracil, used together with surgery, are still advocated

MYXEDEMA

Therapeutically induced hypothyroidism has been recommended in the management of selected cases of congestive heart failure and coronary heart disease In many instances, the results of such therapy have been gratifying, yet spontaneous myxedema may result in cardiac enlargement, pericardial effusion, and even congestive heart failure The relationship of myxedema to elevated serum cholesterol levels and to the development of atherosclerosis is well known, and patients with severe hypothyroidism may experience precordial pain

The classical patient with myxedema is easily recognized because of his placid, sleepy appearance, poor memory, sensitivity to cold, dry, coarse skin, thick lips and tongue; and scant hair with thinning of the eyebrows In contrast, some patients may appear outwardly nervous and distraught, and their behavior may seem manic The diagnosis can usually be established by determining the basal metabolic rate, although this determination may be misleading since the value for "basal" oxygen consumption tends to rise with the onset of congestive heart failure The circulation time is usually prolonged and the serum cholesterol level is markedly elevated in myxedema Anemia is frequently present and has occasionally been confused with pernicious anemia Characteristically, the anemia is normocytic and normochromic, and responds only to thyroid extract

The electrocardiogram exhibits changes which may provide the clue that leads to the diagnosis Characteristically, it exhibits bradycardia, low voltage of atrial and ventricular complexes, and T waves which are flat or inverted The diagnosis can be established by means of I^{131} uptake studies, protein-bound iodine determinations, and hormonal I^{131} conversion ratios The factors which may interfere with these determinations have been discussed in relationship to thyrotoxicosis. Finally, if doubt in the diagnosis persists, a therapeutic test with small doses of thyroid extract may be utilized.

Therapy of myxedema may be achieved with thyroid extract, sodium L-thyroxine, or triiodothyronine. Because of the danger of precipitating attacks of precordial pain, initial dosage should be small and should not exceed ¼ grain of thyroid extract or its equivalent daily Maintenance dosage must be carefully adjusted and should be tailored to the needs of the individual Often, the result obtained may be somewhat less than optimal as far as the myxedema is concerned, however, this is preferable to pushing the dose of thyroid to the point at which the patient's pain becomes a threat to his existence.

PITUITARY AND ADRENAL FACTORS

In the section dealing with the metabolic aspects of congestive heart failure, the roles of the posterior pituitary antidiuretic hormone and of aldosterone in the genesis of congestive heart failure have already been discussed (Chap 3) They are listed at this point merely to include them among the extracardiac factors which play a role in heart disease. In all probability, these factors play such an important role in the development of these manifestations that they should be regarded as a part of the series of physiological responses which occur in the organism during failure of the heart.

NUTRITIONAL DISORDERS

Among the nutritional disorders which may produce cardiac manifestations, beriberi is perhaps the most widely recognized (*see* Part 16, Chap 11) A deficiency of thiamine interferes with glucose metabolism and pyruvate accumulates in the blood and tissues This block in carbohydrate metabolism in the citric acid cycle interferes with energy production by the myocardium and is responsible in part for the production of the manifestations of beriberi heart disease In the usual case, there is a high cardiac output and an increased stroke volume, together with peripheral vasodilatation, a bounding pulse, increased pulse pressure, diminished circulation time, and a decreased arteriovenous oxygen difference Although beriberi heart disease has come to be

ANEMIA

Anemia, which is severe and chronic, may produce cardiac manifestations through several mechanisms (see Part 16, Chap. 11). Cardiac output *is increased to compensate for* the reduced oxygen-carrying capacity of the blood. This can result in cardiac hypertrophy and ultimately in congestive heart failure. If coronary flow fails to increase sufficiently to compensate for the decrease in hemoglobin concentration, the patient may experience attacks of precordial pain. Finally, chronic anemia with its resultant myocardial hypoxia may lead to degenerative changes involving the heart muscle, these may lead to a further decrease *in the reserve of the heart*

The characteristic symptoms of severe anemia include dyspnea, easy fatigability, and palpitation. Precordial pain may occur even in young patients and in the absence of significant coronary atherosclerosis. Peripheral edema may occur but is usually a manifestation of a nutritional deficiency associated with the anemia. Physical examination reveals general pallor, a rapid bounding pulse with a widened pulse pressure, and "hemic" mur*murs, which may be systolic or diastolic in* time. Although the usual *hyperkinetic circulatory syndrome* associated with anemia is widely known and easily recognized, a significant number of patients with anemia may manifest an entirely different adjustment to the decreased oxygen-carrying capacity of the blood. In this group, the heart rate is normal or slow, the velocity of peripheral blood flow is reduced, and cardiac output is normal or low. The precise mechanism by which this alternate mechanism of compensation for chronic anemia develops is unknown.

In the management of patients with cardiovascular disease, the presence of a coexistent anemia *should always be kept in mind and* every effort should be made to establish its cause and to correct it. In treating the anemia itself, it should be recognized that, although transfusions of whole blood may provide the most direct means of correcting the anemia, this procedure may precipitate congestive failure As a result, if blood is to be administered to any severely anemic patient, it should be given slowly, in small volumes, and under constant supervision.

ENDOCRINE FACTORS

Of the various endocrine factors which may influence the state of the circulation. *hyperthyroidism* is probably the commonest *(see Part 16, Chap 10). It should* be suspected in every patient with congestive failure and atrial fibrillation when the ventricular rate fails to respond to adequate digitalization The presence of wide staring eyes, a fine tremor of the fingers, silky smooth skin, weight loss, increased frequency of bowel movements, or a salmon-colored facies, should provide a clue suggesting hyperthyroidism In many instances, however, the presence of an overly active thyroid may be masked, *and a normal sinus rhythm with* a normal heart rate does not necessarily rule out the presence of thyrotoxicosis. The diagnosis of hyperthyroidism may present some difficulty. As suggested above, the symptoms and signs may influence the clinician in the wrong direction The measurement of the basal metabolic rate is often unreliable because of the effect of congestive failure on this determination. The estimation of the thyroid uptake of I^{131} can be helpful but at times may *be misleading. Falsely high values* may occur as a result of iodine deficiency following prolonged dietary salt restriction *Low values* may be obtained when patients have unknowingly received preparations such as *iodides*, sulfonamides, certain mercurial diuretics, or radiographic contrast media When doubt exists, additional laboratory studies should include determinations of the serum cholesterol, the protein-bound iodine, and the I^{131} conversion ratio. Finally, the response of the I^{131} uptake to the administration of thyroid hormone or triiodothyronine may be determined In normal subjects, the uptake of I^{131} is decreased following therapy with thyroid hormone while *in thyrotoxic subjects this* response does not occur

In the presence of excess circulating thyroid hormone, the oxygen needs of all tissues including the myocardium are increased. This increased demand is met by an increase in cardiac output largely effected through an increase in heart rate. It has been *estimated that* some 20 per cent of patients with thyrotoxic heart disease have no underlying cardiac abnormality. In the remainder, cardiovascular

cent above the normal during the thirty-second week. These physiologic adjustments of pregnancy must be kept in mind in patients with organic heart disease who anticipate a pregnancy and in pregnant patients who develop signs and symptoms of congestive heart failure.

PAGET'S DISEASE OF BONE

In Paget's disease of bone, functional arteriovenous fistulas develop in the involved bones resulting in increased regional blood flows. In some cases, significant increases in cardiac output have been reported, and it has been suggested that congestive failure might occur on this basis alone. However, Paget's disease occurs more commonly in patients in the later decades of life, and it is probable that the onset of congestive failure represents the combined effects of a primary cardiac defect and the peripheral arteriovenous fistulas of Paget's disease. Additional functional studies in patients with Paget's disease will be required in order to clarify and quantitate the mechanisms by which this condition influences cardiovascular function.

MUSCULAR DYSTROPHIES

Most descriptions of the muscular dystrophies have been limited to those of the clinical involvement of the skeletal musculature (see Part 16, Chap. 9). However, pathological studies have demonstrated that the myocardium is involved in more than one-half of all autopsied cases, and death has been attributed to congestive failure in more than one-third of all cases. A variety of electrocardiographic changes has been reported during life in such patients, and consist predominantly of tachycardia, short P-R intervals, broad QRS complexes, deep Q waves, and abnormal P waves. Manifestations of congestive heart failure are rarely seen presumably because of the enforced inactivity; however, heart failure may occur suddenly and may be a terminal event in the disease process. Since the pathological changes found in the hearts of such patients are identical with those found in skeletal muscle, every patient with progressive muscular dystrophy should be regarded as a potential cardiac patient and should therefore be treated accordingly.

SUMMARY

A number of factors operating primarily outside of the realm of the heart and the great vessels may indirectly influence the work of the heart or may coincidentally involve the heart and so produce symptoms and signs of heart disease. As a result, it behooves the clinician to be aware of these various factors and to approach the management of every patient with cardiovascular disease with all of these extracardiac factors in mind.

relatively rare in the United States as a result of the general high standard of living and the widespread use of vitamin supplements in various food items, such as white bread, the disease still occurs and the possibility of thiamine deficiency in any patient with congestive heart failure should be kept in mind. The criteria for beriberi heart disease set up by Blankenhorn (1946) continue to be applicable: (1) unclear pathogenesis, (2) history of 3 or more months on a thiamine-deficient diet; (3) signs of peripheral neuritis or pellagra, (4) cardiomegaly with sinus rhythm; (5) edema, high venous pressure, anemia, and hypoproteinemia; (6) minimal electrocardiographic changes; and (7) recovery with decrease in heart size following specific therapy.

An unusual variation of beriberi heart disease, in which acute arterial hypertension developed and congestive heart failure followed, has been described by Walters. It is likely that many atypical cases go unrecognized and, because of inadequate therapy, they may progress to a severe and irreversible stage.

In *cirrhosis of the liver*, the presence of ankle edema, ascites, collateral portal circulation, and vascular spiders, together with a history of an inadequate diet and alcoholism, usually suffice to make the diagnosis Occasionally, however, manifestations of congestive failure are superimposed upon cirrhosis, and these may go undetected. The heart may be involved in the presence of cirrhosis because of intrinsic myocardial disease or it may be influenced because of malnutrition and its allied metabolic defects, the effects of arteriovenous shunts (together with the accompanying increase in blood volume), and the effects of distorted water and electrolyte exchange, perhaps prompted by failure of the diseased liver to inactivate the hormones which normally regulate these moieties Striking enlargement of the heart and obvious congestive failure, however, are uncommon in patients who have cirrhosis in the absence of underlying heart disease.

The adverse effects of *obesity* in reference to cardiovascular morbidity and mortality are well known and constitute an important factor in the establishment of life-insurance actuarial tables In recent years, *a reversible cardiopulmonary syndrome associated with extreme obesity* has been described by several authors. This syndrome includes somnolence, cyanosis, polycythemia, periodic breathing, right axis deviation of the electrocardiogram, and congestive heart failure. In most instances, patients with this syndrome have weighed over 300 pounds and all symptoms and signs have disappeared following the loss of appropriate amounts of weight.

The exact mechanism by which obesity causes the signs and symptoms of this syndrome are unknown. The limited number of studies which have been performed suggest that pulmonary hypoventilation is produced by the mechanical disadvantage of the obesity and that this, associated with periodic breathing, leads to hypercapnia and hypoxia. These in turn result in polycythemia, pulmonary hypertension, right ventricular hypertrophy, and congestive failure Although the mechanisms involved are at present unclear, the clinician should recognize the occurrence of this syndrome and should orient the therapy of the obese patient with these factors in mind.

PREGNANCY

Aterations in cardiovascular dynamics which occur during pregnancy may be interpreted as representing a normal physiologic response to the pregnant state In the patient with a normal heart, these adjustments produce no ill effects, however, in subjects with underlying heart disease, the physiologic alterations of pregnancy may result in severe and sometimes fatal congestive heart failure. The circulatory effects of pregnancy may be noted in the second month of gestation and progress gradually to reach a maximum during the thirty-second week. Thereafter, the intensity of these manifestations declines until the time of delivery Clinically, the effects of pregnancy are manifested by an increased heart rate, palmar flushing, a bounding pulse, capillary pulsations, a prominent apical impulse, and systolic murmurs located at both the apex and base of the heart. Functional studies performed during pregnancy have demonstrated that oxygen consumption increases by 15 to 20 per cent, cardiac output may increase by as much as 50 per cent, the venous pressure rises, and the retention of sodium and water may result in hemodilution amounting to an increase of plasma volume as much as 45 per

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In Paget's disease of bone, functional arteriovenous fistulas develop in the involved bones resulting in increased regional blood flows In some cases, significant increases in cardiac output have been reported, and it has been suggested that congestive failure might occur on this basis alone However, Paget's disease occurs more commonly in patients in the later decades of life, and it is probable that the onset of congestive failure represents the combined effects of a primary cardiac defect and the peripheral arteriovenous fistulas of Paget's disease Additional functional studies in patients with Paget's disease will be required in order to clarify and quantitate the mechanisms by which this condition influences cardiovascular function

MUSCULAR DYSTROPHIES

Most descriptions of the muscular dystrophies have been limited to those of the clinical involvement of the skeletal musculature (see Part 16, Chap 9). However, pathological studies have demonstrated that the myocardium is involved in more than one-half of all autopsied cases, and death has been attributed to congestive failure in more than one-third of all cases. A variety of electrocardiographic changes has been reported during life in such patients, and consist predominantly of tachycardia, short P-R intervals, broad QRS complexes, deep Q waves, and abnormal P waves Manifestations of congestive heart failure are rarely seen presumably because of the enforced inactivity, however, heart failure may occur suddenly and may be a terminal event in the disease process Since the pathological changes found in the hearts of such patients are identical with those found in skeletal muscle, every patient with progressive muscular dystrophy should be regarded as a potential cardiac patient and should therefore be treated accordingly.

SUMMARY

A number of factors operating primarily outside of the realm of the heart and the great vessels may indirectly influence the work of the heart or may coincidentally involve the heart and so produce symptoms and signs of heart disease As a result, it behooves the clinician to be aware of these various factors and to approach the management of every patient with cardiovascular disease with all of these extracardiac factors in mind

relatively rare in the United States as a result of the general high standard of living and the *widespread use of vitamin supplements in* various food items, such as white bread, the disease still occurs and the possibility of thiamine deficiency in any patient with congestive heart failure should be kept in mind. The criteria for beriberi heart disease set up by Blankenhorn (1946) continue to be applicable. (1) unclear pathogenesis; (2) history of 3 or more months on a thiamine-deficient diet, (3) signs of peripheral neuritis or pellagra; (4) cardiomegaly with sinus rhythm, (5) edema, high venous pressure, anemia, and hypoproteinemia; (6) minimal electrocardiographic changes; and (7) recovery with decrease in heart size following specific therapy.

An unusual variation of beriberi heart disease, *in which acute arterial hypertension de*veloped and congestive heart failure followed, has been described by Walters. It is likely that many atypical cases go unrecognized and, because of inadequate therapy, they may progress to a severe and irreversible stage.

In *cirrhosis of the liver*, the presence of ankle edema, ascites, collateral portal circulation, and vascular spiders, together with a history of an inadequate diet and alcoholism, usually suffice to make the diagnosis. Occasionally, however, manifestations of congestive failure are superimposed upon cirrhosis, and these may go undetected. The heart may be involved in the presence of cirrhosis because of intrinsic myocardial disease or it may be *influenced because of malnutrition and its* allied metabolic defects, the effects of arteriovenous shunts (together with the accompanying increase in blood volume), and the effects of distorted water and electrolyte exchange, perhaps prompted by failure of the diseased liver to inactivate the hormones which normally regulate these moieties. Striking enlargement of the heart and obvious congestive failure, however, are uncommon in patients who have cirrhosis in the absence of underlying heart disease.

The adverse effects of *obesity* in reference to cardiovascular morbidity and mortality are well known and constitute an important factor in the establishment of life-insurance actuarial tables. In recent years, *a reversible cardiopulmonary syndrome associated with extreme obesity* has been described by several authors. This syndrome includes somnolence, cyanosis, polycythemia, periodic breathing, right axis *deviation of the* electrocardiogram, and congestive heart failure. In most instances, patients with this syndrome have weighed over 300 pounds and all symptoms and signs have disappeared following the loss of appropriate amounts of weight.

The exact mechanism by which obesity causes the signs and symptoms of this syndrome are unknown. The limited number of studies which have been performed suggest that pulmonary hypoventilation is produced by the mechanical disadvantage of the obesity and that this, associated with periodic breathing, leads to hypercapnia and hypoxia These in turn result in polycythemia, pulmonary hypertension, right ventricular hypertrophy, and congestive failure. *Although the mech*anisms involved are at present unclear, the clinician should recognize the occurrence of this syndrome and should orient the therapy of the obese patient with these factors in mind

PREGNANCY

Aterations in cardiovascular dynamics which occur during pregnancy may be interpreted as representing a normal physiologic response to the pregnant state. In the patient *with a nor*mal heart, these adjustments produce no ill effects; however, in subjects with underlying heart disease, the physiologic alterations of pregnancy may result in severe and *sometimes fatal congestive* heart failure The circulatory effects of pregnancy may be noted in the second month of gestation and progress gradually to reach a maximum during the thirty-second week. Thereafter, the intensity of these manifestations declines until the time of delivery. Clinically, the effects of pregnancy are manifested by an increased heart rate, palmar flushing, a bounding pulse, capillary pulsations, a prominent apical impulse, and systolic murmurs located at both the apex *and base of the heart* Functional studies performed during pregnancy have demonstrated that oxygen consumption increases by 15 to 20 per cent, cardiac output may increase by as much as 50 per cent, the venous pressure rises, and the retention of sodium and water may result in hemodilution *amounting* to an increase of plasma volume as much as 45 per

her arms of a leaden colour, clammy and cold. She could not lye down in bed and had neither strength nor appetite, but was extremely thirsty. Her stomach, legs, and thighs were greatly swollen, her urine very small in quantity, nor more than a spoonfull at a time, and that very seldom. . . . It is now almost nine years since the Digitalis was first prescribed for this lady, and notwithstanding I have tried every preventive method I could devise, the dropsy still continues to recur at times, but it is never allowed to increase so as to cause much distress, for she occasionally takes the infusion and relieves herself whenever she chooses Since the first exhibition of that medicine, very small doses have been always found sufficient to promote the flow of urine.

CLASSIFICATION OF HEART FAILURE

Attempts have been made to define and describe the limits of the many variations observed among patients who have heart failure. Often the products of these attempts take the form of classifications made from one point of view or another. Overlapping of these classifications has occurred, and it is common to find the several groupings listed end to end, as if each entry represented a different kind of heart disease

Forward and Backward Failure. The beginning of failure, before congestion is recognized and before symptoms are noted, has been the basis of pathophysiologic descriptions

Failure of output is a reduction in the flow of blood to the tissues of the body, called *forward heart failure* More completely, the decreased output exerts the effect of decreasing renal blood flow and the glomerular filtration rate, and producing retention of sodium and thereby of water *This effect probably is accomplished via the adrenal cortex and by means of aldosterone*, but the several steps concerned still are not known The succession of steps leads to *hypervolemia* and subsequently to *edema*[1]

Failure of pumping action is the beginning of the train of events described as *backward failure* (Harrison) According to this concept, the venous return is not adequately handled, and systemic venous engorgement occurs The increased venous pressure opposes the oncotic pressure at the capillary level, leading to edema

The concepts of forward and backward failure are justified to the extent that they emphasize part of the mechanism of the formation of edema The importance of the role of retention of sodium and of hypervolemia has been widely accepted (Davis). The terms "forward" and "backward" are, at times, used as if they described clinically different diseases. Thus, backward failure of the right ventricle would produce systemic venous congestion while backward failure of the left ventricle would produce pulmonary vascular congestion. Even though decreased output and increased atrial pressure (congestion) often occur together, it is possible for one of the two phenomena to predominate or even to occur alone This concept, first advanced by experimental workers,[2] was then confirmed in man through cardiac catheterization (Selzer, 1960).

Myocardial and Mechanical Heart Failure. In hemodynamic terms, *myocardial failure* describes the situation in which there is an increase of the end-diastolic volume of the ventricle because of ventricular dilatation with increase of residual blood There is a decrease in effective systolic emptying. However, there is no predictable relationship between end-diastolic volume and end-diastolic pressure over the range of volume increments (Eddleman). The increase of ventricular end-diastolic pressure is necessarily followed by an increase of pressure in the respective atrium and in the veins that are served by it. Thus, increase of diastolic pressure of the left ventricle results in pulmonary congestion, while increase of diastolic pressure of the right ventricle is followed by systemic congestion Myocardial failure includes states in which the myocardium becomes inadequate, either because of diffuse disease of the myocardium, or as a final stage of the clinical course of valvular or septal defects in which the myocardium becomes hypertrophied

Mechanical heart failure implies production of visceral congestion without necessarily involving failure of the ventricular myocardium. Two types of congestion should be considered separately.

1 Constriction of the ventricular wall from without (constrictive pericarditis), within (fibroelastosis), or in the wall itself (amyloidosis, fibrosis) causes an *increase* of diastolic pressure which is followed by atrial and venous

[1] See Chaps 3 and 4, this Part, Editor

[2] See Chaps 1 and 2, this Part Editor.

5

Clinical aspects of heart failure

MILTON W. ANDERSON AND JOHN A. CALLAHAN

INTRODUCTION

Heart failure represents a clinical syndrome due to diverse causes, as well as faulty function of specific segments of the circulation; therefore, the manifestations of this condition are numerous and varied. Separation of symptoms and signs resulting from the causative lesion from those directly connected with the heart failure may be difficult in some instances. In other situations, individual variations of the adaptative phenomena differ in spite of similar causative factors for the failure syndrome, so that the over-all picture differs from patient to patient.

The manifestations of heart failure may appear different depending upon the criteria for evaluation. The clinician recognizes one set of circumstances as representing the syndrome; the laboratory specialist, who determines values for pressure and flow hemodynamically, would recognize different circumstances. Similarly, varied criteria might be set up by the myocardial biochemist or by the nephrologist, who describes the syndrome as it pertains to the role of the kidneys in readjusting salt and water.

One common denominator is *inadequacy of the circulation in one or more parts of the total body circulation for a given person at a given time.* This means that *the cardiac output is inadequate to meet the demands of the body.* When this happens, prior to the development of the syndrome, certain adaptative phenomena, both neurogenic and humoral, as well as those intrinsic within the heart, will have exhausted their ability to maintain a compensated state. As these mechanisms become exhausted, *the cardiovascular system may be said to have progressively lost its reserve.* In some patients, this reserve may be retained for a long period, even though it may be strained to the limit, if that limit is not exceeded. In other patients, the cardiac reserve may be exhausted rapidly by the superimposition of any of several types of stress, which acutely increase the demands of the body, interfere with the adaptive mechanisms, or further compromise the cardiovascular pump.

In most patients, the onset of the syndrome is gradual. The symptoms are first noted during *exertion* or other stressful situations. The failing heart cannot increase its output to meet the greater requirements of the tissues. Later, a more profoundly inadequate circulation leads to symptoms that are evoked with smaller degrees of activity. Some of the variation in the clinical manifestations is related to the speed of onset of heart failure, the different causes for the failure, and differences in the requirements of the organs producing the symptoms and in the metabolic state of the person

The heart is always involved, but sometimes the condition of the heart may not be the principal cause of the failure, the heart has, however, the role of being the dominant organ It influences the resulting disease and is influenced by it.

The classic account by William Withering (1785) beautifully describes the full-blown picture of the syndrome of heart failure:

> I found her nearly in a state of suffocation, her pulse extremely weak and irregular, her breath very short and laborious, her countenance sunk,

her arms of a leaden colour, clammy and cold. She could not lye down in bed and had neither strength nor appetite, but was extremely thirsty. Her stomach, legs, and thighs were greatly swollen; her urine very small in quantity, nor more than a spoonfull at a time, and that very seldom. . . . It is now almost nine years since the Digitalis was first prescribed for this lady, and notwithstanding I have tried every preventive method I could devise, the dropsy still continues to recur at times, but it is never allowed to increase so as to cause much distress, for she occasionally takes the infusion and relieves herself whenever she chooses. Since the first exhibition of that medicine, very small doses have been always found sufficient to promote the flow of urine

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The concepts of forward and backward failure are justified to the extent that they emphasize part of the mechanism of the formation of edema. The importance of the role of retention of sodium and of hypervolemia has been widely accepted (Davis). The terms "forward" and "backward" are, at times, used as if they described clinically different diseases. Thus, backward failure of the right ventricle would produce systemic venous congestion while backward failure of the left ventricle would produce pulmonary vascular congestion. Even though decreased output and increased atrial pressure (congestion) often occur together, it is possible for one of the two phenomena to predominate or even to occur alone. This concept, first advanced by experimental workers,[2] was then confirmed in man through cardiac catheterization (Selzer, 1960).

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Mechanical heart failure implies production of visceral congestion without necessarily involving failure of the ventricular myocardium Two types of congestion should be considered separately.

1. Constriction of the ventricular wall *from without* (constrictive pericarditis), within (fibroelastosis), or in the wall itself (amyloidosis, fibrosis) causes an increase of diastolic *pressure which is follow*ed by atrial and venous

[1] See Chaps. 3 and 4, this Part. *Editor.*

[2] See Chaps 1 and 2, this Part. *Editor.*

congestion. In the case of the left ventricle, pulmonary hypertension is also a result.

2. The narrowing of one of the AV valves causes rise in pressure in the respective atrium and venous system (*mitral stenosis = left atrial* and pulmonary hypertension; tricuspid stenosis = right atrial and systemic hypertension). The normal level of ventricular pressure of these forms and the pressure gradient that develops across the valve are typical of these lesions.

High-output and Low-output Failure. In the average case of congestive heart failure, cardiac output decreases below the level of output that is normal for the particular patient, and usually well below the average normal output for persons of that particular size.

In contrast to this, there is a group of patients with congestive heart failure who have greater than normal cardiac output. This state has been called *high-output failure, hyperkinetic syndrome with failure,* and *overactive heart.* When these conditions are present, even the increased cardiac output cannot meet the metabolic demands of the body. There may be an increased tissue demand, such as arises in *thyrotoxicosis,* a defect in the transfer system, such as occurs in profound *anemia,* or alterations in volume, such as develop in *hypervolemia* and large *arteriovenous shunts* The situation which exists in the presence of *beriberi heart disease* is still incompletely understood. When beriberi is present, there probably are defects in transport systems and in cellular metabolic systems.

Right-sided and Left-sided Failure. Right-sided failure implies failure predominantly of the right ventricle. This is characterized clinically by an increase in systemic venous pressure, venous congestion, and peripheral edema Left-sided failure implies failure predominantly of the left ventricle, and it produces pulmonary vascular congestion Combined right-sided and left-sided failure produces pulmonary vascular and systemic venous congestion In most cases of congestive heart failure, combined failure of both sides eventually comes about.

Cor Pulmonale. This term describes right ventricular strain and hypertrophy as a result of disease of the lungs, the pulmonary circulation, or both An acute form of this condition exists in the case of acute right ventricular strain after *pulmonary embolism.* In the presence of chronic cor pulmonale, the heart disease is the result of disease of the lungs Certain diseases, like ventricular septal defect with pulmonary hypertension, produce an end-stage condition which is similar to that of cor pulmonale. Often the over-all weight of the heart in the diseases which produce cor pulmonale is small, and the hypertrophy of the right ventricle might be overlooked.

Diseases of the lungs productive of chronic cor pulmonale are those which involve the vessels diffusely, such as primary pulmonary hypertension, multiple thromboses, various kinds of fibrosis, and extravascular processes of infiltration and compression. Other diseases are those accompanied by predominant loss of effective pulmonary volume, such as emphysema, asthma, and chronic bronchitis. One additional group includes alveolar hypoventilation, such as *kyphoscoliosis, neuromuscular disease,* and extreme obesity. Obviously, in one patient emphysema and fibrosis or emphysema and hypoventilation can occur together.

Circulatory Failure. Failure or inadequacy of the circulation may occur as a sudden catastrophic event When this happens, symptoms are produced by a profound decrease in arterial pressure and a sudden deficiency in the perfusion of tissues This action, in itself, is not a part of the congestive syndrome. It belongs in the separate category of *circulatory shock* Shock often occurs among patients who have heart disease, and the terms "cardiac shock" or "postinfarction shock" are applied Such a patient is hypotensive, restless, and obtunded, and exhibits a cold, pale, sweaty skin. Many patients suffering from chronic congestive failure manifest this pattern of a profound shock-like state in the last hours of life. Other patients, who have suffered a severe insult, such as a massive myocardial infarct, may display the peripheral signs of shock and have, at the same time, pulmonary congestion or frank pulmonary edema In "cardiac" or "cardiogenic" shock, the most important cause of the syndrome is the sharply decreased cardiac output However, additional factors are represented by various reflexes and by the presence of tissue substances and hormones in the circulating blood, some of them contributing to the alteration while others are ineffective compensatory phenomena

New York Heart Association Classification. The New York Heart Association classification is built upon severity of disease in individual

patients and does not consider causation or type of disease. Many of the classes of this grouping have no relationship to congestive heart failure The classification consists of four functional classes listed by numbers, and five therapeutic classifications listed by letters. Class I includes patients who have no symptoms, class II includes those whose symptoms appear only on exertion, class III applies to patients who have severe symptoms, such as will permit only little exertion, and class IV includes patients who are incapacitated and bedridden

The functional classification describes the amount of exertion the patient can tolerate The therapeutic classification suggests the amount of exertion the patient should undertake and does not presume to describe detailed therapeutic programs Therapeutic class A refers to a patient whose physical activity need not be restricted. Class B describes patients who may be allowed ordinary exertion, but who should avoid extreme exertion Class C describes patients who should exercise moderation, even in ordinary activities Class D describes patients whose activity should be markedly restricted Class E includes patients who should be at complete rest in bed or in a chair The functional and therapeutic classifications need not be parallel. Thus, a man in the first few days after a myocardial infarct might be classified I, E

CLINICAL SYMPTOMS OF CONGESTIVE HEART FAILURE

In most instances, congestive failure develops slowly, not as the immediate result of a catastrophe The first symptoms are experienced during stressful situations, perhaps severe exertion. Later, as the disease becomes more severe, symptoms are produced as a result of less exertion, and eventually they occur while the victim is at rest. The symptoms of congestion are the direct consequences of deficient output and of compensatory mechanisms which the body employs as a result of the deficient pumping The prominent symptoms are breathlessness, weakness and fatigue, cough, abdominal discomfort, swelling of the dependent portions of the body including the abdomen, and mental symptoms

Dyspnea. Dyspnea, or "shortness of breath," is present when the person is conscious of some difficulty in breathing This is a subjective experience and does not always correlate well with the objective signs of congestive failure Many persons may experience dyspnea and not have congestive heart failure. Normal persons may experience dyspnea as a result of unusual exertion. Persons who have no organic disease can be dyspneic because of anxiety.

Dyspnea in the presence of congestive heart failure first occurs *during exertion* and subsides quickly with rest. In patients who have pulmonary hypertension, the dyspnea may remain during a considerable period of rest. In mitral stenosis and some instances of hypertensive heart disease, the severity of exertional dyspnea may remain the same for long periods, with no significant increase. Eventually, the severity progresses with the onset of failure, and dyspnea comes to be present even during rest

In the lungs, mechanical encroachment is produced by the congestion of blood in the pulmonary capillaries, which occupies space ordinarily used for air. The total capacity of the lungs is reduced, this change being manifested mostly as a *reduction in vital capacity.* The turgor of the congested vessels and probably edema of the interstitial spaces produce increased stiffness (reduced compliance) of the lungs The result is an increased work of breathing. The tense, wet lungs cause *exaggerated responses of the stretch receptors in the lungs* Similar receptors in the right heart and great veins, proprioceptive receptors in the muscles of respiration, and the anxiety and excitement of the patient combine with the pulmonary reflexes to produce an increase in respiratory drive In spite of these situations, the alveoli usually are adequately ventilated and arterial blood in the presence of congestive failure often is adequately oxygenated unless pulmonary edema is already present The factors causing the dyspnea often bring about a respiratory effort which exceeds the actual need Therefore, the use of opiates in extreme dyspnea is both physiologic and effectual.

Orthopnea is an extension of dyspnea, although at times a patient may complain more bitterly of orthopnea than of exertional dyspnea Orthopnea results from an actual increase in pulmonary congestion when the patient lies down. Through increase of venous return, redistribution of the volume of circulating blood takes place when a person lies down. This can be observed to produce a decrease in vital capacity

Pulmonary edema usually is a sudden and

potentially catastrophic event in the course of heart disease. It may occur as the result of (1) a sudden change in dynamics of the previously compensated heart; (2) myocardial infarction; (3) acute left ventricular failure in the presence of hypertension.[3] Pulmonary edema may occur during the course of chronic congestive heart failure; when it does, it most often occurs at night. This action seems to combine the change in vital capacity associated with lying down with a change in cardiac output during sleep. The patient experiences severe dyspnea, cyanosis, coughing productive of frothy, often pink, "edema" fluid, and panic. This state requires prompt treatment, and the measures often are surprisingly effective. A less dramatic form of the same process is *paroxysmal dyspnea.* When pulmonary edema is present, the pressure of the blood in the pulmonary capillaries exceeds the colloid osmotic pressure of the blood, and transudation of fluid occurs through the alveolar-capillary wall into the alveolar space. The wet alveolar membrane and the edema fluid interfere with gas exchange. The edema fluid may become frothy and interfere further with gas exchange.

Coughing often is produced as a result of congested lungs and bronchi, and may be an annoying symptom. It may result from pressure of an enlarged pulmonary artery or its left branch on the trachea or recurrent laryngeal nerve. Coughing often robs the patient of badly needed sleep, and it may precipitate an episode of paroxysmal dyspnea or pulmonary edema

Periodic breathing (*Cheyne-Stokes respirations*), due to hypoxia or reduced cerebral blood flow, may be observed in patients who have congestive heart failure. Yet it is by no means specific, since it may occur in many disease states and in some normal states This term describes an alternation between periods of apnea and hyperpnea, often accompanied by stupor and restlessness. During one of the episodes of periodic hyperpnea, paroxysmal dyspnea or pulmonary edema may be precipitated.

Hemoptysis may occur in variable degree, the quantity of blood ranging from faint staining or streaking of the sputum to fatal hemorrhage. The bleeding might come from engorged pulmonary tissue, bronchial mucosa, or a ruptured blood vessel. Hemoptysis is particularly common when mitral stenosis and heart diseases producing pulmonary hypertension are present, or when bronchial infection is present. Obviously pulmonary embolism, common in the course of congestive failure, may be a cause of hemoptysis.

Abdominal Distress. Gastrointestinal symptoms are common among patients who have congestive heart failure, and occasionally such symptoms may be the presenting manifestations. Pain in the right upper abdominal quadrant or epigastrium is common. This may be the type of pain which arises with exertion or which is felt at rest. Usually the liver is found to be enlarged and tender. Rapid *enlargement of the liver* may be painful, and occasionally it may suggest an acute abdominal emergency. Because of other factors, which are poorly understood, there is no predictable relationship between height of venous pressure and enlargement of the liver or abdominal symptoms

Other abdominal symptoms may include *anorexia, nausea,* and *vomiting* as a result either of engorgement of abdominal viscera or of medication. When *dependent edema* and abdominal enlargement with *ascites* are extensive, the abdominal symptoms may abate after some time, even though the ascites and abdominal engorgement may not be completely relieved. The abdomen seems to possess a certain degree of accommodation to the new state of dysfunction. Usually there is a gradual loss of body tissue which goes unnoticed because of the edema. Over a long period, *cachexia* may be marked.

Edema. The accumulation of edema fluid in the dependent parts of the body is the classical feature of congestive heart failure. Congestive failure was only later separated from the condition manifested by the general group of edematous patients said to have "dropsy." The phrase "edema-laden" sometimes is used to emphasize the picture of wetness and swelling in patients with severe congestive heart failure As a rule the clinical discovery of edema is not difficult Occasionally it is difficult to distinguish *between* the edema of heart disease and that of other origin. Abdominal swelling and ascites sometimes will cause diversion of diagnostic scrutiny away from heart disease.

The problem of edema brings up the ques-

[3] Pulmonary edema is described in detail in Chaps. 10 to 14, this Part *Editor.*

tions, "What is the first event in congestive heart failure? In what sequence does the heart decompensate?" An integral part of these questions is, "What produces the edema?" This problem returns to a consideration of the hypotheses of "backward" and "forward" failure as mentioned above Under the designation "backward" failure, it was contended that the primary event is elevation of venous pressure, elevated capillary pressure, and formation of edema Other factors were acknowledged as contributing to the edema fluid (Barger; Davis and Smith). Under "forward" failure, an attempt was made to emphasize the role of the kidney in the formation of edema. Early in the course of heart failure, increased reabsorption of sodium occurs, primarily as a result of altered cardiac output The mechanism which initiates renal retention of sodium is not clear, but it may involve part of the normal reflex and humoral adjustments for the maintenance of blood pressure An important role certainly is played by *aldosterone*, with a direct effect on the renal tubular transport of sodium, and therefore of water (Davis).*

Cerebral Symptoms. Symptoms of cerebral dysfunction are parts of the advanced stages of congestive heart failure These occur late in the progression of decompensation of the heart, but such a sequence might require only a relatively short time in cases of serious and rapidly advancing disease, such as massive myocardial infarction The symptoms are those of inadequate perfusion of the brain, probably combined with more *complicated* secondary effects of inadequate perfusion of other organs of the body Mild changes in personality and periods of confusion and disorientation appear relatively earlier Restlessness, stupor, and coma may precede death These symptoms are profoundly influenced by many medications used in the treatment of congestive heart failure It would be well to review therapy carefully if a change in the state of consciousness or behavior *develops*.

CLINICAL SIGNS OF CONGESTIVE HEART FAILURE

The causes of congestive heart failure are varied This fact is influential in producing the first manifestations of congestive heart failure in different chambers. It is thereby possible to relate certain clinical observations to failure of specific cardiac chambers, especially in the early course of the syndrome. Traditionally, clinicians divided congestive heart failure into *left heart failure* and *right heart failure*. Synonyms of left heart failure also are the terms, "left ventricular failure" and "left-sided heart failure." Similar expressions have been applied to failure limited to the right side of the heart. A more exact classification and interpretation of the clinical aspects of congestive heart failure are possible when the hemodynamic abnormalities producing these findings are related to the specific chamber in which the pumping function is impaired. This concept appears valuable, even though it is immediately apparent that it is rare for the syndrome of congestive heart failure to be caused by failure limited to one chamber. Hence, this section will be confined to a description of the clinical signs and findings as they appear to the examiner at the bedside.

Left Ventricular Failure. Failure of adequate left ventricular output may occur acutely secondary to massive infarction, acute inflammatory myocardial disease, or sudden inadequacy of the aortic or mitral valves. This type of failure occurs *less dramatically* after progressive hypertrophy secondary to (1) systemic arterial hypertension, (2) stenosis and regurgitation of the aortic valve, (3) mitral valvular regurgitation, or (4) less acute loss of myocardial function as a result of coronary atherosclerosis or myocarditis.

Clinical examination of the patient who has left ventricular failure readily yields indications of an abnormal cardiac status as well as abnormality in areas remote to the heart Hypertrophy and dilatation of the left ventricle are detected by palpation of a sharp apex impulse lateral to the left midclavicular line Percussion of the precordium will confirm a broad area of cardiac dullness, sometimes extending to the left midaxillary line *In* the presence of both acute and chronic left ventricular failure, a *diastolic gallop rhythm* frequently is heard at the apex [Fig 18-4(1)], the 3d, or adventitious, *heart sound* appearing at the time of rapid ventricular filling Functional incompetency of the mitral valve related to left ventricular enlargement, with dilatation of the mitral valve ring, frequently is responsible for a *blowing apical systolic murmur* Extracardiac evidence of left ventricular failure also may be

* See also Chap 3, this Part *Editor*

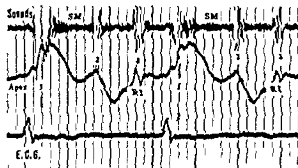


Fig. 18-4(1). Protodiastolic gallop sound (3) occurring between the 2d sound (2) and the 1st sound (1). This coincides with the rapid inflow wave (RI) of the apex linear cardiogram. The soft decrescendo systolic murmur (SM) of mitral insufficiency is noted. This electrocardiogram demonstrates atrial fibrillation.

noted. Peripheral cyanosis related to increased difference in arteriovenous oxygen saturation is especially observed in the presence of acute left ventricular failure when cardiac output decreases rapidly. The peripheral pulses usually are rapid and thready, and *pulsus alternans* can be demonstrated when left ventricular myocardial function is severely impaired. Pulsus alternans is detected as an alternately strong and weak impact against the examining fingers palpating the peripheral pulse in the presence of a regular cardiac rhythm. Left ventricular failure manifests itself most dramatically by *congestion of the lungs* on the basis of simultaneous left atrial failure.

As a consequence of any acute or chronic etiologic factor, when left ventricular diastolic pressure increases, a similar increase in pressure must ensue in the left atrium to maintain a left atrioventricular filling gradient. The increased blood volume and consequent pressure are reflected back to produce pulmonary venous and pulmonary capillary hypertension. As indicated before, more blood pooled in the lungs will reduce the compliance and air capacity of these structures. At the point at which the pulmonary capillary pressure exceeds that of the colloid osmotic pressure, transudation into the lungs and pleural spaces takes place.

Characteristically, the patient who has uncontrolled and overt left ventricular failure assumes a sitting position in bed, and often will rest on his hands to hyperextend the thoracic sector of the spinal column. He complains of suffocation when he is in a recumbent position. His breathing is rapid and labored, and he uses accessory muscles to increase respiratory excursions. These signs, orthopnea and tachypnea, are first noted in response to unusual effort or emotion, and they will subside as the stressful situation ceases. When the clinical state is severe and acute pulmonary edema develops, a fulminating picture presents itself. The patient will be cyanotic and restless and will perspire profusely; his breathing will be extremely rapid, punctuated by frequent coughing, which often is productive of copious amounts of frothy and blood-stained sputum.

Usually, a *rapid heart rate* is present. *Atrial fibrillation* often is the rhythm in patients whose causative lesion is deformity of the mitral valve, as well as in a high percentage of patients who have advanced left ventricular failure arising from other causes. Generally, the *2d cardiac sound* in the pulmonic area will be characterized by increased splitting and accentuation of the pulmonic component. Results of auscultation over the fields of the lungs vary greatly, depending upon the stage of the congestive syndrome. There may be essentially normal breath sounds, despite an increased respiratory rate. When left ventricular failure is chronic and mild, *fine moist rales* limited to the lower segments of the lungs are the rule.

Musical and sibilant rales heard diffusely in all areas, especially in the expiratory phase of respiration, are characteristic of the acute pulmonary congestion which manifests itself as *paroxysmal dyspnea* (older term: *cardiac asthma*). This clinical picture may mimic closely that of bronchial asthma unless additional diagnostic signs are at hand.

In chronic failure of the left heart, which is associated with pleural effusion, the breath sounds over the sites of the retained serous collections will be diminished or absent, and the percussion note will be flat. Acute pulmonary edema presents the listener with a multitude of sounds, including moist rales, expiratory wheezes, and coarse, bubbling rales and rhonchi from tracheal secretions.

Roentgenograms of patients who have left ventricular failure will show a diversity of pathologic changes.[5] Characteristically, enlargement of the left atrium is present as a significant abnormal feature of the cardiac silhouette when mitral valvular disease is at

[5] See Chap. 8, this Part. *Editor*

hand, and, to a lesser extent, when the morbid state is left ventricular failure without primary mitral disease Chronic pulmonary venous hypertension, like mitral stenosis, frequently is accompanied by the roentgenographic demonstration of costophrenic septal lines. The pulmonary fields show variable evidence for the congestive changes that exist [Fig. 18-4(2)]. *Hilar vascular congestion* is seen routinely and extends to cast bilateral central infiltrative shadows when pulmonary edema also is present Bizarre forms of pulmonary congestion, which may be limited to one lung or to one aspect of one lung, may cause left ventricular failure to be confused with other pulmonary pathologic processes, such as neoplasm or inflammation [Figs. 18-4(3 and 4)]. Similarly, the occurrence of serous effusions may be limited, and the effusive processes may be located at sites which make a differential diagnosis difficult.

Perhaps the only specific electrocardiographic abnormality attributed solely to left atrial enlargement is the appearance of broad P waves of increased amplitude in both the extremity and precordial leads The electrocardiogram also may confirm the presence of atrial fibrillation and will reflect left ventricular hypertrophy, necrosis, or other abnormality, such as conduction disturbance, when the causative lesion has primarily affected the left ventricular myocardium Right ventricular and right atrial enlargement also may be observed in chronic left heart failure, which produces right ventricular hypertrophy and, finally, right ventricular failure. All these electrocardiographic abnormalities also may be present to some extent in patients whose condition has not reached the decompensated state, so that they do not make it possible to assume the presence of congestive failure. *Electrical alternans*, on the other hand, is an infrequent electrocardiographic finding that correlates highly with left ventricular failure [Fig 18-4(5)]. This phenomenon exhibits itself by alternate ventricular complexes of either greater amplitude or greater duration in the presence of sinus rhythm.

Right Ventricular Failure. Elevated right ventricular diastolic pressure, which is the salient evidence of right ventricular failure, most frequently results from left ventricular failure, which has interfered with forward flow from the right ventricle. Right ventricular failure occurs as a primary event on the basis of outflow obstruction caused by both pulmonary valvular obstruction and pulmonary vascular disease, which increases resistance to right ventricular outflow Acute right ventricular failure arising from *embolization of the pulmonary arteries* is dramatic when severe, and characteristically is featured by tachypnea, diaphoresis, restlessness, systemic hypotension, and cyanosis The clinical picture resembles that of acute hypoxia, which indeed is present If death is not immediate, with massive pulmo-

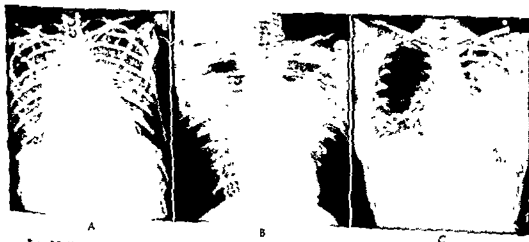


Fig 18-4(2) Roentgenologic manifestations of *pulmonary edema* A. Bilateral involvement, generalized throughout both pulmonary fields, usual type B Bilateral involvement, limited to the upper parts of the pulmonary fields, "bat's wing" or "angel's wing" distribution C. Unilateral involvement.

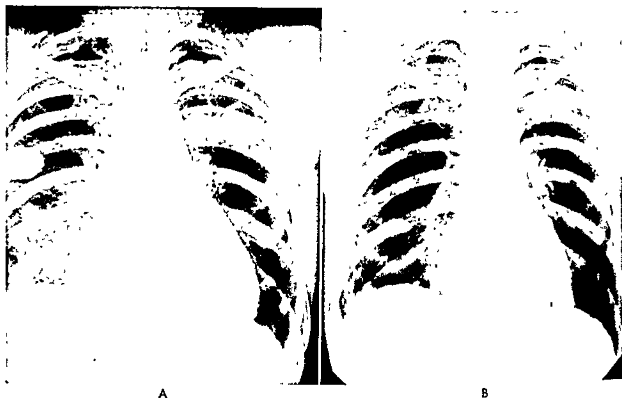


Fig. 18-4(3). Interlobar pleural effusion (vanishing tumor of lung). Unusual roentgenologic manifestation of pleural effusion (A), which disappeared promptly after treatment of congestive heart failure (B)



Fig. 18-4(4). Pulmonary congestion which produced minimal symptoms and was thought to be malignant infiltrate (A). Treatment for congestive heart failure resulted in clearing of the pulmonary fields (B).

nary embolism, signs of right ventricular dilatation and acute pulmonary hypertension will appear. The observations include palpable and visible pulsation over the pulmonary artery in the 2d interspace in the left parasternal line. A *pulmonic systolic murmur* and increased amplitude and splitting of the 2d heart sound are heard in the same area The roentgenographic and electrocardiographic findings which suggest acute cor pulmonale appear in other sections of this publication [6]

Chronic right ventricular failure may predominate over left ventricular failure in patients who have generalized myocardial disease, such as thyrotoxic heart disease, myocarditis, or infiltrative myocardiopathies Right ventricular failure occurs exclusive of left ventricular failure on a "mechanical" basis as a result of the overwork resulting from prolonged severe volume overload associated with congenital septal defects, or the pressure overload imposed by pulmonic valvular or infundibular stenosis or pulmonary hypertension. When right ventricular failure is superimposed on preexisting left ventricular failure, amelioration of distressing pulmonary symptoms and findings will ensue, presumably reflecting reduced right ventricular output, which is more readily accepted by the failing left ventricle

The signs of chronic right ventricular failure include evidence of hypertrophy and dilatation of that chamber Since the structure is anteriorly located, there will be widening of the area of cardiac dullness upon percussion, and a diffuse precordial heave will be both palpable and visible Frequently, as in left ventricular failure, a diastolic gallop sound is heard at the time of rapid ventricular filling in the 3rd left interspace near the sternum or over the xyphoid A *systolic murmur* produced by tricuspid regurgitation, when that valve becomes incompetent, is best heard over the lower part of the sternum and at the left parasternal area The murmur characteristically is louder in full inspiration (Rivero Carvallo).

Inability of the right ventricle to accept venous return, which is augmented by hypervolemia secondary to the renal mechanisms for retention of salt and water, produces peripheral signs The veins of the neck are distended with blood, even with the patient in a sitting position, indicating greater venous volume and

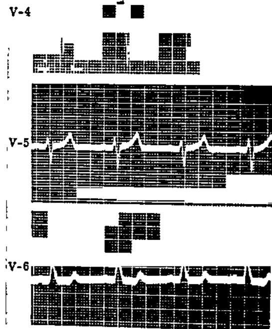


Fig 18-4(5) Electrical alternans Alternate complexes have significantly different amplitude of the QRS complex Left precordial leads are from a patient who had coronary sclerosis.

pressure. An *a* wave predominates in the jugular phlebogram when the tricuspid valve remains competent. This can be detected clinically by the observation that the a wave is not simultaneous with the carotid pulse.

Incompetence of the tricuspid valve, which occurs readily in the presence of right ventricular dilatation, permits systolic regurgitation of right ventricular blood into the right atrium The new systolic wave that is generated is not absorbed by a capillary bed or stopped by other valvular action before it can be recognized in the systemic veins This wave can be observed *in the veins of the neck* to coincide with ventricular systole, and, when incompetence of this valve is extreme, it will even produce visible pulsations in the veins of the dorsum of the hands and also will generate palpable pulsations *in the engorged liver.*

A *peripheral type of cyanosis* caused b[illegible] is noted in the presence of severe right ventricular failure When right ventricular failure is secondary to chronic pul-

[6] See Part 13, Chap 8. *Editor*

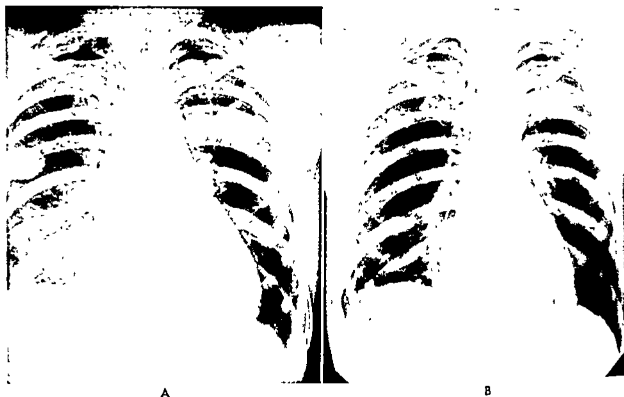


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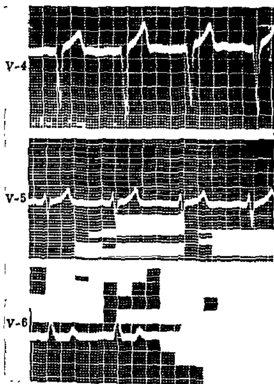


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A *peripheral type of cyanosis*, caused by reduced cardiac output and greater extraction of oxygen by the tissues as a result of the slowed circulation time, is noted in the presence of severe right ventricular failure. When right ventricular failure is secondary to chronic pul-

[a] See Part 13, Chap 8 *Editor*

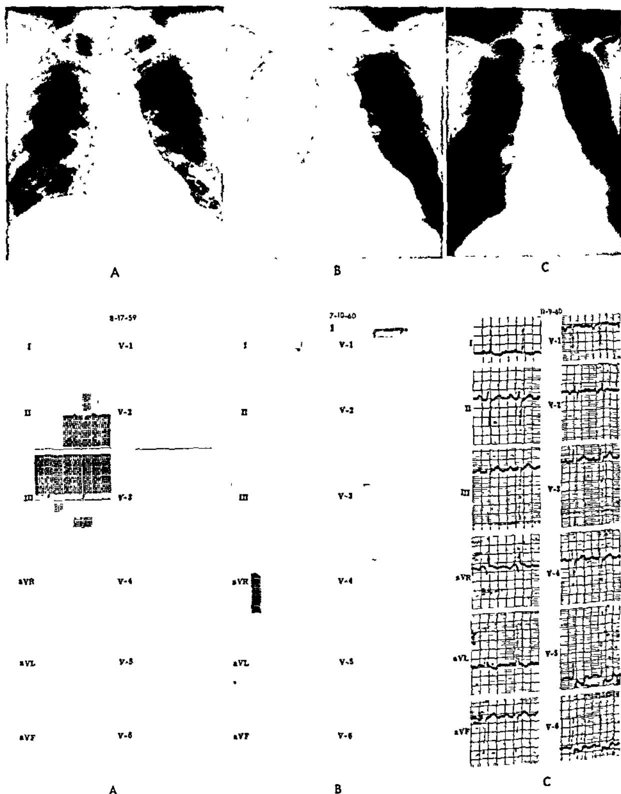


Fig. 18-4(6). Evaluation of congestive heart failure. Pairs of representative roentgenograms and electrocardiograms made from a 62-year-old man who experienced the sudden onset of free aortic regurgitation. A. Acute pulmonary congestive changes and small pleural effusions present about 1 month after the onset of the symptoms of acute dyspnea and hemoptysis The cardiac silhouette was small and the electrocardiogram was normal at this time. B The same patient about 10 months later, when his clinical state had become stabilized by medical management. The roentgenogram has shown moderate enlargement of the cardiac silhouette, with prominence of the left ventricle. The pulmonary fields are now free of visible congestion in the roentgenogram. The electrocardiogram demonstrates increasing left axial deviation and left ventricular hypertrophy plus the effects of digitalis. C Roentgenogram and electrocardiogram made approxi-

monary disease which causes arterial anoxia, *mixed cyanosis* occurs, it may be extreme.

Signs of dropsy in the presence of congestive heart failure usually denote right ventricular failure, but a similar picture occurs in obstruction of the tricuspid orifice secondary to tricuspid stenosis or atresia or to right atrial tumors A similar clinical picture may also be produced by chronic constrictive pericarditis, pericardial effusion, or neoplasms, which selectively interfere with venous return to the right heart

There will be a total decrease in effective cardiac output, which initiates the well-known retention of fluid characteristic of the dropsical state Venous pressure is increased at first intermittently, with periods of increased cardiac work, but finally constantly as myocardial function deteriorates further. Prior to overt failure of the right heart, manual pressure over the engorged liver will visibly distend the veins in the neck, indicating inability of the right atrium to accept a greater return This is called the *hepatojugular reflux* Venous hypervolemia that cannot be accepted by the right atrium causes increased venous pressure The elevated venous pressure interferes with normal osmotic gradients in the systemic capillary beds, causing extracellular accumulation of fluid

The first clinically recognizable features are a *gain in weight* and a *decrease in the output of urine* Only later, after considerable gain in weight, does *edema* become evident at clinical examination in the form of pitting of the extremities The venous and capillary bed are filled to a higher pressure and, in a sense, edema in the tissues aggravates the tension in venous channels by increasing the rigidity of the tissues The increased venous pressure causes or helps perpetuate the edema Thus, the edema and venous pressure are both cause and effect, once the decompensation is under way When effective treatment is instituted, venous pressure remains elevated above normal until diuresis brings about a reduction in blood volume

Peripheral edema is first noted about the shoe tops of the ambulatory patient at the end of the day, and will disappear overnight as a result of nocturnal diuresis or redistribution A similar type of edema of the pitting variety may appear first over the sacrum, buttocks, and thighs, or will be indicated by deep grooves made by the pressure of clothing over dependent parts of the body in the case of bedfast patients Later, this edema may proceed to generalized *anasarca*, with massive subcutaneous collections of fluid in the legs, genitals, lower abdominal walls, and even in the arms and hands, if they remain dependent much of the time The edema is typically soft, it dents under pressure and is painless, but it may be accompanied by oozing, even through the intact tightly stretched skin, when the condition is extreme. Selective accumulations of fluid in serous cavities are common, although the reasons for the selective site in individual patients remain obscure. Characteristically, *ascites*, which may at times be massive, is seen more frequently in constrictive pericarditis and tricuspid obstructive lesions than in generalized heart failure which originates in the left ventricle. The accumulation of *serous effusions* in the pleural spaces and also in the pericardial sac will intensify already impaired pulmonary ventilation and cardiac inflow and output, so that removal of these collections frequently will ameliorate symptoms

The liver becomes enlarged early in the course of right heart failure. The size and tenderness of the structure vary with the state of congestion Prolonged *congestive hepatomegaly* and also sudden insult to the liver occurring in acute congestion will cause jaundice in some patients A combination of icterus and peripheral cyanosis produces a distinctive discoloration of the skin in patients who have congestive failure caused by tricuspid stenosis These patients are found to have direct-reacting hyperbilirubinemia, as opposed to the infrequent appearance of the "retention" type of jaundice which may accompany pulmonary infarction complicating congestive heart failure When right heart failure is of long duration, *splenomegaly* also may be present.

Combined Failure of Left and Right Sides of Heart. A multiplicity of signs indicating that congestive failure has involved both the left side and right side of the heart most often is encountered clinically. Any attempt to outline

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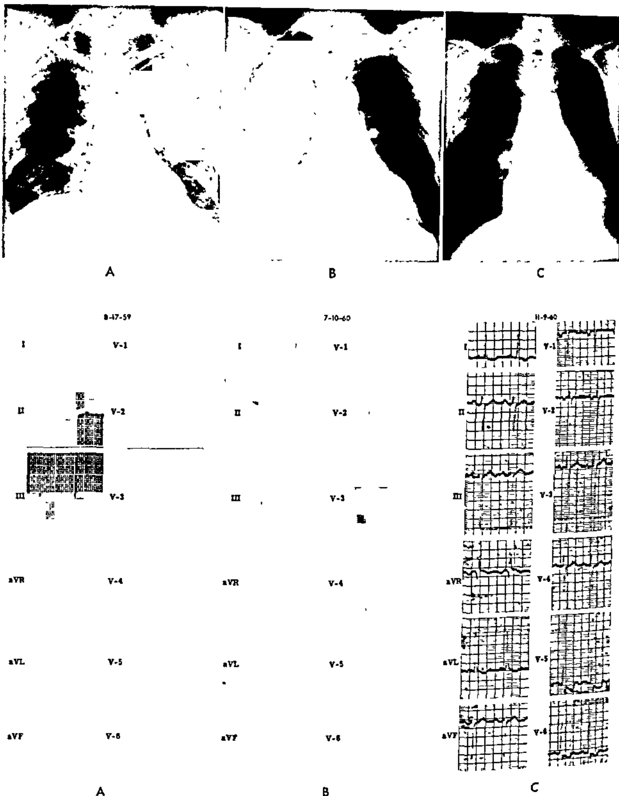


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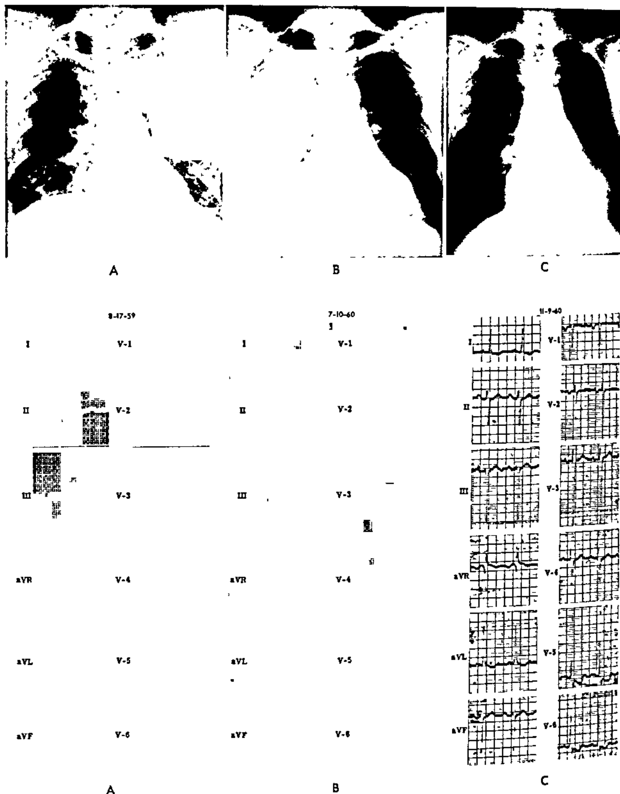


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6

The blood in heart failure

STEPHEN C. MATHEWSON AND MARIO STEFANINI

The clinical findings and the blood changes encountered in patients with heart failure are the final effects of several major mechanisms. The decline in contractile energy of the myocardium leads to dilatation of the cardiac chambers, increased residual blood volume, and elevation of the intraventricular end-diastolic pressure. Changes in venous pressure and in the distribution of blood in various parts of the body follow promptly. The alterations in the pulmonary and systemic circuits often result in congestion and edema, and lead finally to increased volume of blood, and of interstitial and perhaps intracellular fluid. Irrespective of right-sided or left-sided failure, the circulation time becomes prolonged and tissues become hypoxic.[1]

Hypoxia and, especially in right ventricular failure, the elevation of venous pressure, probably lead to sodium retention by the kidney because of decreased renal blood flow and decreased glomerular filtration rate. More active secretion of aldosterone and desoxycorticosterone by the hypoxic adrenal gland may also contribute to increased tubular reabsorption of sodium. Finally, the hypothalamus may secrete greater quantities of antidiuretic hormone. It is perhaps significant in this respect that substances inducing retention of salt are, in fact, found in the urine of patients with congestive heart failure (Singer and Wener). Hypoxia also stimulates the bone marrow, possibly through increased production of erythropoietin by the kidney and other organs. It also affects adversely the nutritional status of the vascular intima, lesions of which may lead to increased incidence of venous and arterial thrombosis. The liver, because of its proximity to the right atrium, bears the first brunt of right-sided heart failure. Its congestion is often more marked than that of other organs (Popper and Schaffner).[2] The hepatic involvement may lead to deficient protein synthesis involving albumin and, occasionally, some of the coagulation factors and it will be discussed later. Thus, the effects of hypoxia are of great complexity because of the functional involvement of many organs.

The hematologic changes observed in congestive heart failure are of a wide variety. They are apt to be more pronounced when congestion follows constrictive pericarditis or tricuspid valve disease. In such cases, the rise in the peripheral venous pressure is greater and severe hepatic involvement is more frequently found. On the other hand, hematologic changes are less severe when the failure of the right ventricle follows failure of the left; and this condition is more commonly seen. The pathogenesis of the hematologic changes in heart failure is, in most instances, of difficult interpre-

[1] Because of the dissociation properties of oxyhemoglobin, *the arterial oxygen tension*, which is considerably decreased, is a better indication of hypoxia than oxygen saturation of peripheral blood, ...ly slightly decreased.

[2] The severe hypoxia does not necessarily imply failure of function. In fact, needle biopsies of the liver in thirty patients with varying degrees of heart failure due to a variety of causes have shown no correlation between histological changes, severity and duration of the heart failure, and the results of liver function tests (White et al.).

signs without including the symptomatology of heart failure and without excluding features peculiar to the specific cause is faulty, but it appeared to be justified in the foregoing paragraphs to bring about a better understanding of the whole syndrome.

Roentgenograms of the thorax and electrocardiograms made during examination of a man 62 years old are illustrated in Fig 18-4(6). They demonstrate the evolution of the total syndrome of congestive heart failure, beginning with left ventricular failure secondary to acutely acquired aortic valvular regurgitation. Initially, this patient experienced hemoptysis and severe recurring pulmonary congestion characterized by tachypnea, orthopnea, and the physical signs of pulmonary edema. Progressive left ventricular hypertrophy became evident electrocardiographically as well as in the roentgenograms His clinical state was then stabilized for several months. The observed improvement was short-lived, however, and once more left ventricular dilatation developed, accompanied by functional mitral regurgitation It was followed by right ventricular failure The latter manifested itself prior to death, and was accompanied by hepatomegaly and generalized anasarca.

THERAPY

The treatment of congestive heart failure is reviewed in detail elsewhere [7] but, since it has a profound influence on symptoms, will be mentioned here The early use of digitalis by Withering, as noted above, profoundly altered *the symptoms and appearance of his patient.* The therapeutic measures in use today are effective and are responsible for a changed course in patients who have congestive heart failure. It is now possible to maintain patients in a state of supported compensation, but the classical state of sodden swelling may return quickly if treatment is stopped Under treatment, patients may function efficiently, but they subsist in a state of buttressed normalcy, and patient and physician must remember the extent of this state of dependence A patient often can be maintained in an edema-free state until the very late stages of heart disease, and he may escape, for some time at least, the consequences of chronic congestion The patient who has congestive heart failure ought to have the benefits of a short instruction program on the nature of his illness and the properties of his medications. It is hoped that he will also come to know the names of the medications. This type of instruction is far from universal. Some patients stop the use of medication as soon as they improve. Others are inadequately treated and are allowed to retain a greater or lesser amount of edema as a chronic situation Any patient, even one who is under the most careful scrutiny, might experience a change in his total state at some time. Actually, the course of congestive heart failure and the appearance and disappearance of symptoms deserve closer scrutiny than they did before effective therapy became available. When a new symptom appears or a new difficulty is encountered, the whole therapeutic regimen should be reviewed The physician should ask himself, "Is this a new development in the course of the disease, or has this been produced by medication?" He should also ask, "Is there any curable basic or contributing disease, the curing of which might relieve or ameliorate the congestive heart failure?"

[7] *See Chap 15, this Part Editor*

ure has subsided If bleeding develops, higher and more sustained doses of vitamin K are needed to counteract the hypoprothrombinemic effect of Dicumarol and analogs

On the other hand, *thromboembolic phenomena are common in patients with congestive heart failure* In a recent series, thromboembolic manifestations were found at autopsy in 30 per cent of 565 patients with congestive heart failure due to rheumatic heart disease (Griffith et al) A reverse study (Hampton and Castleman) indicates that 30 per cent of 370 autopsied patients who showed significant pulmonary embolization had suffered from heart disease, often with congestive failure These results are not surprising Many of the factors mentioned previously may precipitate venous thrombosis in congestive heart failure. They include slowing of blood flow with prolongation of the circulation time, hypervolemia, increased venous pressure, high blood viscosity linked to the high red cell mass, and others Their combined effect leads to stagnation of blood within the veins and, thus, to local hypoxia Endothelial damage follows, in the authors' opinion one of the major factors in venous thrombosis This picture becomes exaggerated in bedridden patients Clinicians are aware of the frequent formation of clots within the veins of the lower limbs in these patients, clots from which thrombi may extend proximally in the direction of the venous flow and achieve considerable length before severe embolism occurs In fact, repeated episodes of pulmonary embolization may occur without any or with only circumstantial evidence It is of interest that pulmonary embolization may be suspected in patients with congestive heart failure purely on the basis of a hematologic finding, *the sudden appearance of normoblasts in the peripheral blood.* Recently, the authors have become aware of a syndrome which also seems to bear relation to the occurrence of pulmonary embolization during congestive heart failure. The syndrome refers to patients whose congestive heart failure is rapidly progressive and resistant to digitalization, even at or near toxic doses, or to mercurial diuretics (Tench) The ligation of the superficial femoral veins in these patients, even when there is no clinical evidence of peripheral thrombosis, may be followed by a striking diuretic response It would seem that there is, in these cases, a continuous seeding of the pulmonary vascular tree with multiple, small emboli responsible for intractable heart failure, a process which is reversed by the ligation of veins.

An equally interesting aspect of intravascular clotting in congestive heart failure is *the occurrence of mural thrombi in the left atrial cavity* with consequent systemic arterial embolization The opposite, of course, also occurs In a published series, at least 30 per cent of patients with rheumatic heart disease, atrial fibrillation or mitral valve disease (or both), and arterial embolization presented some degree of congestive heart failure (Daley et al.). Like cyanotic congenital heart disease, congestive heart failure sees the frequent occurrence of thrombotic as well as (more rarely) hemorrhagic manifestations Both conditions are accompanied by significant and important changes in the formed elements of the blood and in the protein composition of plasma. The discussion presented in this chapter emphasizes the fact that the mechanism of these changes is quite complex and, at least in part, obscure.

tation primarily because of widespread *ignorance of the mechanisms involved in the control* of human hematopoiesis. Studies with dye and radioactive techniques (Schreiber et al.) *concur to indicate that the total blood volume is greatly increased in congestive heart failure.* This increment involves both red cell mass and *plasma volume but the extravascular volume is* also greatly increased. In fact, while the increase in plasma volume hardly ever surpasses *50 per cent or so, the volume of interstitial fluid* may often be doubled. The increase in plasma volume is, as mentioned, probably related to *the retention of salts and fluids* The stimulus for the increased red cell mass is probably the effect of tissue hypoxia (Part 6, Chap 8). *These* abnormalities *tend* to return to normal as the heart compensates, spontaneously or because of therapy The bone marrow appears *hyperactive. There is hyperplasia of all series,* especially of the erythroid elements More mature elements predominate The overactivity of *the bone marrow is reflected in* changes of the formed elements in the peripheral blood Hemoglobin level, red blood cell count, and hematocrit *reading are elevated to* various degrees Reticulocytes are higher than normal (1 to 2 per cent), while orthochromatic and polychro*matophilic normoblasts may be found in the* peripheral blood There is leucocytosis with neutrophilia and moderate shift to the left of *the granulocytic series. Slight thrombocytosis is* found in a majority of cases while thrombocytopenia is found only occasionally The blood *sedimentation rate is elevated (McGinnis et al)* unless the red cell mass is considerably increased, in which case the value may be very low In the authors' experience at least, RBC survival times determined with Ashby's technique have been normal in a majority of cases. Slight increase in urinary and fecal urobilinogen and moderate elevation of the indirectly reacting bilirubin may be found Associated as they are with normal RBC survival time and elevated retention of BSP, these findings probably indicate *moderate liver dysfunction* because of congestion and hypoxia. Blood ammonia level may be high and, thus, account for a variety of mental symptoms occasionally found in patients in failure (Bessman and Evans). Total serum proteins and albumin fraction are often decreased, and the albumin/globulin ratio may be inverted. These changes are probably related to the poor nutritional status, the decreased protein synthesis by a hypoxic liver and, when present, peripheral edema and formation of effusions. Relative increases in gamma and beta globulin fractions are reflected by the occasional positivity of the cephalin-flocculation and thymol-turbidity tests. Serum *alkaline* phosphatase may also be elevated. There is no general agreement or uniformity of findings with regard to the behavior of the *clotting* factors in congestive heart failure. The concentration or activity of most clotting factors is usually normal, more rarely, it is increased Significant fibrinogenopenia and deficiency of labile factor, less pronounced hypoprothrombinemia, and deficiency of stable factors are occasionally *encountered in the* course of congestive heart failure. They have a complex pathogenesis. A factor in their de*velopment is the poor synthesis of coagulation* agents because of functional involvement of the liver. Another is, possibly, the extensive intravascular *coagulation that may occur* in congestive heart failure due to various factors, particularly within the pulmonary district. *Intravascular clotting means* utilization and depletion of circulating clotting factors Thus, at times, a paradoxical combination of *hypocoagulability of the blood* and of *intravascular clotting* is observed Further evidence for a process of intravascular clotting in these pa*tients is the finding* that the patient's serum may contain a factor which accelerates the formation of plasma thromboplastin

In any case, as compared to congenital cyanotic heart disease, spontaneous bleeding manifestations are rare in congestive heart failure, even during and after surgical procedures The one exception comprises patients who have developed severe polycythemia In such cases, the same factors which have been described for congenital heart disease come into play, and significant bleeding may be encountered Another practical consideration refers to the use of "anticoagulant" therapy with "antiprothrombin agents" *Patients with congestive heart failure and hepatic congestion are highly sensitive to the effects of Dicumarol and analogs, possibly because of the slow rate of synthesis of clotting factors by a hypoxic liver* Thus, these drugs should be used cautiously and with careful control of the plasma prothrombin time until such time as heart fail-

than to suspected masked hyperthyroidism for which no laboratory confirmation could be definitely ascertained [1]

Universal Heart Failure (Right and Left Heart Failure). In the course of left-sided heart failure, the right ventricle may become fatigued for a variety of causes which include augmented work due to increased pulmonary resistance, pulmonary hypertension, and hypoxia; then right ventricular failure, as evidenced by subjective symptoms and by a characteristic venous pressure curve, develops The circulation times with ether (to measure the "arm-to-lung" time), with Decholin, calcium, or saccharin (to measure the "arm-to-tongue" time), and with carbon dioxide or nitrogen inhalation (to measure "lung-to-systemic capillaries" time) will reveal the presence of universal retardation of flow in all segments of the lungs However, there are many exceptions, especially as they concern the measurement of the "arm-to-lung" time In a considerable number of cases including hypertensive, arteriosclerotic, rheumatic, and luetic disease, the "arm-to-lung" time has been normal despite the presence of frank right heart failure with a high venous pressure and a positive hepatojugular reflux The "arm-to-tongue" time and the "lung-to-tongue" time (the saccharin time–ether time difference) were invariably prolonged

In a general way, circulation-time studies in congestive heart failure have proved of value in the evaluation of predominant retardation of flow in certain segments of the circulation Unless it can be established that a prolonged circulation time may represent improper mixing and dilution of the test substance in the increased residual blood of a dilated heart, the increased circulation time or the reduced speed of blood flow must be regarded as indicating heart failure which results from a slowing of blood flow in the distended intrathoracic vessels and in the dilated cardiac chambers. Added to this significant factor must be that of the diminished force of the heart which is revealed by diminished cardiac output.

[1] Increased circulation speed has been found by others in cases of pulmonary edema and explained as the result of stimulation of sympathetic centers Actually, this increase may be the determining cause of pulmonary edema because it provokes a "relative" failure of the left ventricle *Editor*

Right Heart Failure. In right heart failure secondary to extensive bronchopulmonary disease, the "arm-to-lung" time is invariably increased (10 to 18 sec), but strangely enough, in some instances is at the upper limit of normal (8 sec). In all these cases, the "arm-to-tongue" time may be increased depending, of course, upon the degree of retardation of blood flow in the arm-to-lung segment. The "lung-to-tongue" time is usually normal (from 5 to 10 sec) which indicates that the functional integrity of the left heart is undisturbed There are rare instances in which, because of severe hypoxia and coronary insufficiency, the left side of the heart becomes functionally handicapped. Consequently, impaired left ventricular function may result as the outcome of long-standing right heart failure. Under such conditions, both the "arm-to-lung" time and the "lung-to-tongue" time yield abnormally prolonged circulation times

There are cases of *decompensated cor pulmonale* of various origins which, in the end stage of chronic pulmonary insufficiency, present considerable interest from the standpoint of circulation-time measurement. The patients, who appear gravely ill, are usually admitted to the hospital as emergencies because of acute bronchopulmonary infections. The clinical features are intense cyanosis, polycythemia, dyspnea, and congestive failure. The circulation times with ether and Decholin seem in marked contrast with those obtained in less critically ill cardiac patients who yield circulation times more markedly prolonged Thus, the "arm-to-lung" time in a "black cardiac" may range from 10 to 16 sec while the "lung-to-tongue" time will yield a reading which is within the normal range of 6 to 10 sec, indicating a predominant right heart failure

7

Circulation times in heart failure

WILLIAM M. HITZIG

AVERAGE TYPE OF CONGESTIVE HEART FAILURE (LOW OUTPUT FAILURE)

The circulation time measured through the lungs in congestive heart failure is invariably prolonged because of the increase in the size of the intrathoracic vascular bed (*i.e.*, the volume of blood in the heart and lungs) and because there is a decline in cardiac output. The degree of prolongation is proportional to the size of the bed In general, it may be said that, the more prolonged the circulation time, the more seriously ill is the cardiac patient. However, this is not universally true. Not infrequently, the patients with cardiac disease who appear most ill are those, suffering from decompensated cor pulmonale, who have circulation times which have been less prolonged than those in patients who appeared less gravely ill but in whom the circulation time measurements showed more extreme deviations from the normal.

Left Heart Failure. In left heart failure, the "arm-to-lung" time may be within normal range whereas the "lung-to-tongue" time is almost always prolonged, sometimes to three times the normal value. *This shows that the prolongation of the "arm-to-tongue" time is localized to the section of the left heart or that the retardation is due to slowing of pulmonary blood flow downstream to the arterial capillaries of the lung (lung-to-tongue segment).* In such cases of isolated left ventricular failure, the normal systemic venous pressure curve and the normal "arm-to-lung" time testify to the functional efficiency of the right ventricle at rest. In other cases, however, even though the venous pressure curve may remain within normal limits, the ether time may be moderately prolonged, occasionally reaching as high as 14 to 16 sec. This may occur particularly when left ventricular failure is severe, the left ventricle and atrium are severely dilated, and pulmonary engorgement is pronounced This bilateral retardation of blood flow, as measured by the circulation-time methods mentioned above, involves both the right and left ventricular units, and reveals thereby a uniformly inadequate or widened cardiopulmonary pathway. The abnormal ether time ("arm-to-lung" time) in such instances may already be significant of "incipient" failure of the right side of the heart. It indicates that, although the right ventricle is able to maintain a normal systemic venous pressure, it is unable to maintain a normal blood velocity through the widened circulatory pathways of the lungs. On the other hand, the prolongation of the "arm-to-tongue" time does not always parallel the severity of the other symptoms of left ventricular failure. In exceptional cases, the "arm-to-tongue" and the "arm-to-lung" time may be within normal limits despite severe symptoms of left ventricular failure Such paradoxical findings were encountered by the author in two cases of pulmonary edema suffering from malignant hypertension. Normal venous pressure was present but there was no explanation for the inconsistency with the clinical picture. There was no anemia or arteriovenous fistula, or other findings consistent with high output failure. A marked tachycardia was present in both instances but this was attributable to heart failure rather

of the high resistance type The vascular dilatation may start in the pulmonary veins, as is the case in early mitral stenosis *In conditions of pulmonary vascular engorgement, the lung markings are well defined and the lung fields are clear* None of these alterations indicate cardiac decompensation, rather, they may express increased filling and elevated pressure on the arterial or venous side as regulatory phenomena If the stasis, however, extends into the smaller vessels (arterioles, venules, and capillaries) which cannot be seen as individual shadow bands, general haziness will cover the entire lung field This condition is usually no longer distinguishable roentgenologically from pulmonary congestion with extravasation of fluid into the pulmonary tissue.

PULMONARY CONGESTION AND SLOWLY DEVELOPING EDEMA

The vascular trunks become still wider, an irregular fine network covers the greater portion of the lung fields and extends to the periphery, *Kerley lines C;* the general haziness increases, particularly in the lower lung fields, while the apical regions are much less involved The vascular shadows lose their distinct contours The hilar shadows become still bigger,

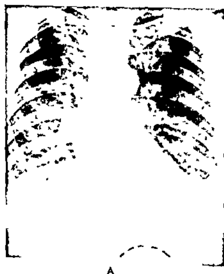




Fig 18-5. *Pulmonary* congestion and edema in heart failure A Man, aged 69 years, with precordial pain and no history of myocardial infarction *The hilar* shadows are irregularly increased, *streaky blotchy* shadows extend to the bases, leaving the upper halves of the lung fields clear Considerable pleural effusion drowns the lower portions of the *heart. On the left,* the large distance between the *gastric gas* and the clear lung indicates the large amount of effusion After 2 weeks of bed rest and proper treatment, lung and pleura *were dry.* B. *Man,* aged 42 years, first diagnosed *as a case* of pneumoconiosis in a man with dust exposure *Mitral stenosis* was eventually diagnosed Chronic small *patchy edema* was almost evenly distributed, only the right lower segment is shown close up Also several horizontal septal *lines (interlobular* edema) are visible No rales were *heard After* mitral valvuloplasty, the lung became perfectly clear.

Roentgenology in heart failure

FELIX G. FLEISCHNER

The terms "chronic lung stasis" (Cooly and Sloan), "central congestion" (Sylla-Zdansky), "pulmonary venous congestion," "chronic passive congestion," and others, are used sometimes with gradual distinctions, sometimes interchangeably It appears to be useful, however, to distinguish the *overfilling of vessels*, arteries and veins, *without "leakage" of fluid* into the interstitial *spaces* and alveoli, from *the condition with* such escape of fluid, the *first condition* may properly be called *pulmonary vascular engorgement, or plethora,* the latter, *pulmonary congestion*. Both these conditions may occur acutely or they may be chronic. The first, vascular engorgement, may become "congestion," and this may deteriorate by sudden or gradual transition to full pulmonary edema This distinction between pulmonary vascular engorgement and pulmonary congestion is useful and should be attempted, even though transitional stages may occur and the distinction cannot be made, in every instance, on clinical and roentgenologic evidence

The causative factors do not generally influence amount and arrangement of edema fluid in such a gross morphologic way as to become distinguishable on the roentgenogram, though certain peculiarities occur in mitral stenosis, glomerulonephritis, the nephrotic syndrome, cor pulmonale of high resistance type, and marked emphysema Three factors, however, appear to influence the location of extravasated transudate and its roentgenologic appearance. (1) anatomical differences of the central and peripheral portions of the lung, (2) differences of the ventilatory excursion of the lung, and (3) the force of gravity. The first two factors will be discussed in connection with acute pulmonary edema. The third, gravity, influences the distribution of blood and tissue fluid even in the systemic circulation. Its effect is greater upon the pulmonary circulation with its low arterial and venous pressures. Not only the venous drainage, but also the lymph drainage of the lower and posterior portions of the lung occur against the influence of gravity In addition, the self-cleansing of the bronchial tree is easily interfered with in those dependent portions, adding obstructive atelectasis and drowning. All these are more marked in the presence of impaired ventilatory excursion. "Hypostasis" of old, obviously comprising all these disturbances, expresses the clinical fact that the dependent portions of the lung are preferentially affected by disturbances of the circulatory and ventilatory systems

PULMONARY VASCULAR ENGORGEMENT

Arterial hypertension in the pulmonary circulation, the result of increased resistance in emphysema, fibrosis, embolism, advanced mitral stenosis, or primary pulmonary hypertension, can produce demonstrable changes by dilatation of the larger branches of the pulmonary artery with or without accompanying dilatation of the pulmonary artery trunk. In this way, the hilar arteries become wider and plumper and also sometimes their main branches are widened. Often these arterial shadows show visible, i.e., increased (intrinsic) pulsations, as evidence of the greater systolic and pulse pressures. Large rounded shadows near the hilus, corresponding to dilated arteries in head-on view, show also distinct systolic expansive pulsations. All these vascular structures, though enlarged, are sharply defined, and the lung fields are clear or even abnormally translucent, as in emphysema or cor pulmonale

The preference of these changes for the dependent lung fields and an accompanying small pleural effusion, often revealed only by the thickened lesser interlobe, or a meniscus in the posterior costophrenic angle, may point in the right direction. One should be aware that borderline pulmonary congestion may be present without any obvious clinical signs and symptoms, even in the presence of normal circulation time

The amount of transudate in the lung may rapidly recede and completely disappear On the other hand, in chronic pulmonary congestion of cardiac origin, the strands of the increased lung markings may become thinner and regain their sharp definition Dense streaks and patches of consolidation, representing *fibrosis* and *hemosiderosis*, but also localized *transudate*, may now appear against the clear background of the rather dry lung of chronic *congestion*

PULMONARY CONGESTION IN AN EMPHYSEMATOUS LUNG

Emphysema counteracts the development and roentgenographic appearance of congestion and edema. In *bullous emphysema, the* total amount of *pulmonary tissue, including* the capillary-carrying alveolar walls, *is* considerably diminished, there are not enough *engorged* capillaries to provide for a hazy background, and engorgement, as far as it occurs, is overcompensated by preexisting *oligemia of* emphysema Furthermore, because *of the* scarcity of tissue there is *hardly* enough matrix for interstitial engorgement. *Therefore, in* marked emphysema, *pulmonary congestion* does not develop to any considerable degree, and stasis may easily escape *roentgenological detection If* the emphysema does not involve *the lung* in an even fashion, if only one lobe has large *bullae, or if* the emphysema involves only one lung, *the* congestive state may still be recognized in other portions On the other hand, the uneven or asymmetrical distribution may distract from the correct interpretation.

IRREGULAR ARRANGEMENT

While the roentgenographic diagnosis of pulmonary congestion and acute pulmonary edema in their *symmetrical* distribution is usually readily made, *transudate* may be distributed *in an* irregular fashion. Several causes for irregular distribution may be listed in addition to localized severe emphysema Edema accumulates when the lymph drainage cannot cope with the amount of fluid leaking from the capillaries. It has been shown by roentgen-pathological correlation and assumed from animal experiments that inflammatory lymphatic obstruction (Altschule, 1949) may be a contributory factor in the accumulation of transudate. In a lung where a previous pneumonic-pleuritic process has left a damaged lymph draining system, the drainage may still be sufficient under otherwise normal conditions In the case, however, of borderline cardiovascular decompensation, the injured area would accumulate edema, while the intact lung with its competent lymphatic drainage might still be kept dry Inhibited ventilatory excursion may also favor accumulation of transudate *in this* area Also, bronchial obstruction may accelerate transudation These factors, and probably also gravity, contribute to lobar, *unilateral, or* otherwise irregular distribution of pulmonary edema *In such a case,* with the loss of the "*normal distribution,*" *it is* sometimes impossible to discern from a single roentgenographic examination whether such irregular shadows are caused by congestion and edema, or by inflammatory infiltration

HEMOSIDEROSIS

In chronic pulmonary congestion, particu*larly in mitral* stenosis, considerable amounts of hemosiderin are frequently deposited *in the* lung The pigment is often arranged in nodular *fashion* causing a miliary picture on the roentgenogram. In rarer earlier stages, the iron pigment is sometimes deposited in and *along the greater interstices,* particularly the inter*lobular septa,* causing septal lines Occasionally, minute *(pea-sized)* irregular round shadows of calcific density are encountered. *preferentially in* the lungs of patients with mitral *stenosis. They* are more numerous in the lower lung fields and may be observed *to grow in size* over many years They are made up of well-organized bone and have been called *tuberous osteomas* (Salinger) Their occurrence does *not parallel* the degree of hemosiderosis, though *they too* seem to be a late product of blood extravasation, indicating *a not* yet fully understood response of *the lung* in mitral stenosis They should not be *mistaken for* in-

ill-defined, and cloudy; confluent shadows extend down to the lower lung fields, obscuring the contours of the cardiac silhouette (Fig. 18-5A). It becomes impossible to obtain "a *picture with good definition and contrast.*"

The increase in number and width of the vascular shadows is caused by their overfilling and widening. The general over-all haziness is due to *engorgement of the arterioles, venules, and capillaries.* In addition, the loss of clear contours and the over-all haziness are due to *increased moisture in the tissues,* and engorgement and distention of the perivascular, *peribronchial, septal, and subpleural lymph* vessels The hilar and perihilar lymph nodes are engorged with transudate (Zdansky). When the over-all congestion is limited, the combination of swollen blood vessels and lymphatics, and spotty interstitial and alveolar transudate, produce a *miliary appearance* remarkably similar to that of pneumoconiosis or even miliary tuberculosis. The patient whose x-ray films are seen in Fig. 18-5B had a long history of dust exposure and was treated for some time for pneumoconiosis before the mitral stenosis was recognized. After successful valvuloplasty, the fleck-like accumulations of edema, *surprisingly constant for a long time* and completely silent on auscultation, disappeared. Edema fluid causes rales only if it is located in alveoli, bronchioles, and bronchi; *interstitial moisture is silent to auscultation.* In other instances of prolonged stasis, interstitial fibrosis and hemosiderin deposits, appearing in a similar way, are of permanent nature, even in a dry lung and with good cardiac compensation.

CHRONIC PULMONARY EDEMA

There is sometimes a gradual transition from marked pulmonary congestion to a certain type *of pulmonary edema. The collections of transudate* in the parenchyma coalesce to larger areas of irregular, ill-defined accumulations of local edema, indistinguishable from pneumonic foci or from infarcts. This rather common type of pulmonary edema, superimposed upon or accompanied by signs of pulmonary vascular engorgement, is usually seen in congestive failure as it may occur in advanced mitral valve disease, hypertensive heart disease, myocardial insufficiency, and other disorders On the roentgenograms, the dense areas of maximal outflow of transudate are located about the hilar regions and lower lung fields and there is, in addition, coarse widening of the vascular shadows down to the diaphragm and the *peripheral lung fields. Isolated* small and large cloudy blotches of edematous infiltration may be seen anywhere else. However, they are rare in the upper lung fields Pleural effusion, preferentially on the right, is common.

The diagnostic difficulties are not exhausted with this systematic listing of the roentgen appearance of pulmonary vascular engorgement, congestion, and edema Clinical history and *present evidence of cardiovascular disease,* and roentgen evidence of abnormal size and shape of the heart and large vessels, should always lead to the consideration that pulmonary and pleural changes might be related to the cardiovascular condition. It is understood, however, that pulmonary congestion and edema may occur in patients whose hearts are of apparently normal size and shape Nevertheless, it is not uncommon that a heart of apparently normal size by standard measurement, may turn out to be moderately dilated, if compared with a previous chest film or with a later one, after recovery from congestive failure. It is some*times difficult to distinguish* dilated hilar arteries from enlarged lymph nodes or from a central consolidation, pneumonic or neoplastic. It is the shape and architecture of the shadow *mass,* and its expansile pulsation, not always distinguishable from transmitted pulsation, that mostly permit the identification. In addition to fluoroscopy, *laminography* may be helpful in proving the vascular nature of the mass and the freedom of the bronchi Bronchography, bronchoscopy, and, in rare instances, angiocardiography may be necessary to determine or exclude the vascular character of these shadows. The difficulties of the differential diag*nosis are still greater* with streaky, reticular, and small nodular or miliary formations in the peripheral lung fields: acute and chronic congestion, fibrosis, and hemosiderosis on the basis of chronic congestion; furthermore, the host of inflammatory, pneumoconiotic, hyperergic, and neoplastic changes has to be considered. Only careful weighing of all clinical evidence, including the observation of changes over short intervals, with or without treatment directed toward congestive failure, may reveal their congestive nature.

9

Special forms of heart failure

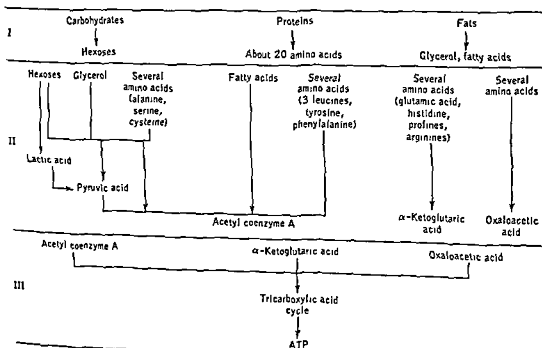
ROBERT M. P. HEGGLIN

HEART MUSCLE METABOLISM IN CARDIAC FAILURE

The term "heart muscle metabolism" refers to the chemical changes taking place in the myocardium during its muscle activity, i.e., during systole and diastole, these changes are required to produce sufficient energy for cardiac action at the needed time The heart muscle metabolism can be considered as twofold (see Part 2, Chaps. 1, 2, and 3) One can study (1) the chemical processes leading to the production of the most important phosphate compound, adenosinetriphosphate, ATP (production of energy), or (2) the processes taking place during contraction, a phase in which there is consumption of energy (utilization of energy).

From previous experimental results (mainly by Bing), it has been observed that, in the failing myocardium, disturbances occur in both phases, i.e., in production and utilization of

The Three Main Phases of Energy Production (after Krebs)



flammatory scars of tuberculosis or histoplasmosis

SEPTAL LINES

Horizontal linear shadows are often observed in the lower lateral lung fields. They are 1 to 3 cm long, about 1 mm wide, strictly horizontal, and spaced 0.5 to 1 cm apart. First described by Kerley (Kerley's lines B), they have been shown to be cast by interlobular septa, thickened by iron impregnation or edema (Fleischner and Reiner). In slightly advanced pulmonary hemosiderosis, iron pigment is occasionally arranged in and along interlobular septa, this fixed pigment lends itself to reliable roentgen-anatomical identification. More commonly, and in all instances of changing width and appearance, these septal lines are caused by *interstitial edema* in these septa, this is known to occur without appearance of edema in the alveoli and bronchioles (Parker and Weiss; Hayward). They do not correspond to individual engorged lymph vessels, as it was previously believed, though lymphatic stasis is a part of congestion and edema, and contributes to their roentgenographic appearance (Zdansky). The observation of these lines, their increase and decrease, presents a practical yardstick of the amount of abnormal moisture in the lung in many instances of beginning, subsiding, or borderline pulmonary congestion Though they correlate statistically with pulmonary arterial hypertension and more closely with capillary or venous hypertension, these septal lines are hardly indicative of any particular one of these hemodynamic irregularities beyond their general relation to the circulatory disturbances incident to pulmonary congestion and edema

PLEURAL TRANSUDATES

Pulmonary congestion and edema are often accompanied by *pleural effusion* Sometimes pleural effusion is the only apparent roentgenographic sign of congestion in the lesser circulation. This may be the case in glomerulonephritis with acute hypertension Small effusions are often arranged between the lung and diaphragm, and not visible as such in the usual anteroposterior view. A small fluid meniscus may fill the costophrenic angle, this is better seen in the oblique or lateral position A small effusion may also be seen on fluoroscopy when the patient bends over laterally to the examined side (*Hessen's maneuver*). Somewhat larger amounts of fluid surround the lung, the coat becoming thinner at higher levels This causes the usual shadows rising along the lateral chest wall with ill-defined upper contours. When the lung is congested, the presence and amount of pleural effusion often cannot be correctly assayed. A roentgenogram taken with a horizontal beam while the patient is in lateral decubitus will reveal the fluid arranged along the dependent chest wall. Unless fluid is encapsulated, this examination reveals fluid otherwise detained between lung and diaphragm, and permits a fairly exact estimate of its quantity. The observation of the interlobar fissures, particularly of the lesser "interlobe" (horizontal fissure), is quite helpful. Even small amounts of fluid, when otherwise invisible, become visible as thickening of the interlobe.

If the general pleural space is obliterated, transudate may be poured out into an interlobar pocket and cast a spherical or oblong shadow, usually easily recognized in its nature by its topographic relation to the interlobe, and by fine spicules extending into the fissure on either side. With improvement of the congestive failure, these shadows become narrower and disappear ("vanishing tumors").

Transudate developing in acute pulmonary edema or in the presence of ascites, such as in the nephrotic syndrome or constrictive pericarditis, has a great tendency to assemble exclusively between lung and diaphragm or in the cardiophrenic angle, causing misleading pictures of cardiomegaly, elevated diaphragm, or tumor On the left, the increased distance between the gastric air and the lung base readily suggests the presence of fluid in the diaphragmatic pleural space while, on the right, a "high diaphragm" and wavy shaking of the "diaphragm" seen on fluoroscopy raise a similar suspicion. *With a film* exposed while the patient is in the lateral decubitus, the diagnosis is readily established

9

Special forms of heart failure

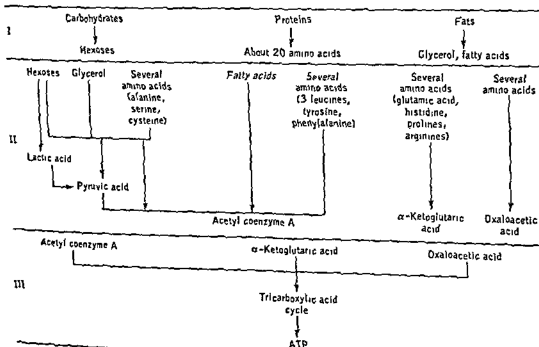
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From previous experimental results (mainly by Bing), it has been observed that, in the failing myocardium, disturbances occur in both phases, i.e., in production and utilization of

The Three Main Phases of Energy Production (after Krebs)



energy. Different forms of heart failure may take place according to the phase of metabolism which becomes abnormal. Cardiac metabolic studies try to correlate the symptoms of myocardial insufficiency with their causes, as this has been done with other clinical syndromes.

In *hypoxia*, ATP cannot be sufficiently built up. A decreased supply of oxygen to the heart muscle due to poor vascularization is an important cause of long-lasting cardiac insufficiency, especially if there is hypertrophy of the left ventricle. In *localized hypoxia* (coronary sclerosis) the parts of the heart muscle which are not involved are sufficiently supplied with oxygen. Actually, such a deficiency of oxygen as would cause insufficient production of energy is rare.

THE METABOLIC DISTURBANCES OF CARDIAC FAILURE

Theoretically, there are many possible causes for the disturbances of energy production or energy utilization. Though much progress has been made, knowledge concerning clinical forms of cardiac failure is still far from clear. The disturbance may consist of (1) abnormal synthesis of ATP due to disturbance of oxidation, lack of enzymes, or inhibition of enzyme activity (*disturbance of energy production*), or (2) abnormal synthesis of actomyosin, ionic imbalance, or changes in membrane permeability (*disturbance of energy utilization*).

The task of the future will be to identify the disturbance of myocardial metabolism present in any particular form of cardiac insufficiency and to correlate biochemical data with the clinical signs.

Disturbance of Energy Production. The simplest example is that of an extreme anoxemia (asphyxia). Complete blocking of the oxidative processes completely prevents the synthesis of ATP. Accordingly, the amount of ATP decreases in progressive total anoxemia (Schumann). After several minutes of anoxemia, the content of ATP in cardiac muscle is completely exhausted. The synthesis of ATP anaerobically through glycogenolysis is not sufficient to cope with the demand Clinically, this type of heart failure corresponds only to *an acute hypoxia*

Chronic hypoxia of the whole myocardium is clinically rare This would require extremely reduced oxygen tension in the blood, sluggish blood flow through the coronaries, or an increased oxygen demand by the tissues *Hemorrhagic shock* offers an example of disturbance of the production of energy by decreased oxygen consumption.

By means of catheterization of the coronary sinus, Bing showed that, in hemorrhagic shock (both in the oligemic and the normal phase), oxygen consumption is considerably reduced This is supposed to be caused by decreased coronary flow, since the oxygen intake was found unchanged. On the other hand, pyruvic acid utilization diminished, apparently due to the destruction of the cocarboxylase under anaerobic conditions, while lactic acid utilization was not impaired.

Animal experiments proved that decrease in oxygen consumption may also occur in extensive infarcts (Bing). Experimentally, coronary occlusion is not identical with myocardial infarction and is undoubtedly more extensive, as proved by the fact that the fall of blood pressure in Bing's experiments is 50 per cent greater than in clinical conditions In Bing's experiments, oxygen consumption decreased immediately after occlusion. In about half of the experiments, glucose and pyruvic and lactic acids were no longer taken up by the heart muscle, so that they appeared in increased amounts in the venous blood, while potassium and the inorganic phosphate were increased. These metabolic disturbances were transient and could be observed only immediately after the occlusion.

These metabolic processes are basically similar to those found in experimental ventricular fibrillation Lactic acid is found in large quantity in the coronary venous blood, indicating an extremely severe hypoxemic disturbance. According to the degree of hypoxemia, the pyruvic and lactic acid metabolism are differently influenced. In the most severe forms, lactic acid is formed through glycogenolysis (high level in the blood of the coronary sinus); in less severe cases, only the breakdown through cocarboxylase is diminished, due to destruction under anaerobic conditions (medium levels in the coronary venous blood).

In *beriberi heart*, synthesis of ATP is impaired because of the deficiency of thiamine which cannot be phosphorylated to cocarboxylase As there is not enough cocarboxylase, pyruvic acid cannot be utilized and broken

down by the citric acid cycle Therefore, pyruvic and lactic acid appear in the blood stream in increased quantities.

In *diabetes mellitus*, cardiac metabolism is typically changed Glucose utilization is diminished regardless of the high level of blood sugar. Also lactic and pyruvic acid utilization are decreased in the heart muscle, especially the former (Ungar et al). An impaired phosphorylation of thiamine to cocarboxylase is suspected (Foa et al , Siliprandi). On the other hand, the utilization of ketone bodies is increased (from 5 to 9 8 per cent, Bing). In human diabetes, utilization of fatty acids is especially increased Apparently fatty acids are stored in the heart muscle. Bing states that, in the diabetic heart, "there is a disturbance of energy production without diminished cardiac strength" in spite of the above-mentioned changes in myocardial metabolism It is difficult to separate clinically heart failure caused by diabetes from that due to the frequently associated coronary lesions On the other hand, in a diabetic patient, there also are ECG changes in the absence of failure (Q-T-U changes) which are more pronounced in the energeticodynamic type of failure and become more severe if coma supervenes

Disturbances of Utilization of Energy. The cardiac metabolism of congestive failure has been studied for a long time, though only in heart-lung preparations, by physiologists and experimental pathologists This experimental setup reproduces only approximately the conditions of slowly developing heart failure, and the conclusions reached cannot be used for clinical applications.

INVESTIGATIONS ON OXYGEN CONSUMPTION OF THE FAILING MYOCARDIUM The Starling law, founded on isolated heart studies, has dominated the clinical field for a long time According to this law, the oxygen consumption of an isolated heart under constant chemical conditions and constant temperature is determined by the diastolic volume, and thus by the initial length of the muscle fibers Since this length is increased in the failing heart, it was generally assumed that an increased oxygen consumption occurred in clinical cardiac insufficiency Using the catheterization of the coronary sinus (a method which allows a comparison of the coronary venous and arterial bloods and thus offers a direct picture of cardiac muscle metabolism), Goodale found that oxygen consumption of the failing heart increased somewhat per unit of weight. However, Bing did not find any changes Bing and Lorber explain this difference between the acutely failing isolated heart and the gradually decompensating myocardium of human beings by the fact that the volume-energy correlation of the myocardial fibers differs from that of the normal heart The fact that the decompensated heart under stress responds with an increased oxygen consumption supports this assumption It is questionable whether oxygen consumption can be correlated to the weight of the heart muscle because, in hypertrophied hearts, more or less extensive foci of fibrosis simulate a diminished oxygen consumption (naturally these foci do not contract and use little oxygen) while the insufficient fibers utilize more oxygen At any rate, the oxygen consumption of the failing heart is not decreased, as could be expected by virtue of impaired energy production

THE ENERGY-RICH PHOSPHATES IN INSUFFICIENT HEART MUSCLE. The total ATP content has been investigated in decompensated hearts but the results were not conclusive In an isolated insufficient heart, the ATP content was not changed (Wollenberger), in severe intoxication, it was found elevated On the other hand, the energy-rich phosphate compounds were determined in hearts of people who died in heart failure. The great majority of authors found a significant decrease in ATP as compared to the normal heart (Cowan, Herrmann, Linegar et al.). These results are to be interpreted cautiously since ATP is broken down very rapidly post-mortem, and it is impossible to know what occurs in every case before death Hypoxia, at any rate, causes a rapid and extensive decrease of ATP.

UPTAKE OF BASIC SUBSTANCES BY THE INSUFFICIENT HEART MUSCLE In eight cases of cardiac failure, Bing found that there is no statistically significant difference in the uptake by the cardiac muscle of glucose, pyruvic acid, lactic acid, amino acids, and ketone bodies.

INTERPRETATION OF METABOLIC DETERMINATIONS IN CONGESTIVE HEART FAILURE No significant metabolic changes have been found in

human hearts with evidence of congestive failure, in regard to either consumption or uptake of basic substances. As the uptake of these substances is not diminished, it has been concluded that, in congestive failure, *the disturbance depends upon the utilization of energy and not its production.* Bing considers this disturbance to be in the contractile proteins of heart muscle. However, in congestive heart failure, the myocardial fibers do not work under normal conditions. The requirements are always increased, either in order to overcome an increased arterial pressure, to compensate for valvular lesions, or to compensate for decrease of functioning muscle fibers (myocardial infarction, myocardial fibrosis, or myocarditis). This means that the disturbance in heart failure is not always in the proteins, but is due to an overloading of the cardiac fibers which goes beyond the level of good performance so that there are increased energy requirements during normal energy production. Therefore, the problem has to be viewed not as one of disturbed energy consumption, but as one dealing with more than physiological efficiency This problem must be considered, not as one of total cardiac activity (which is diminished in cardiac failure), but as one based on the work efficiency of the individual heart fibers, a parameter which cannot be figured out in individual cases Although, in congestive failure, the total cardiac activity is decreased, the activity of individual, still-functioning fibers may well be increased It has yet to be determined whether, in congestive failure, *additional factors are involved* which affect the myocardium and diminish the contraction (particularly hormonal and neurovegetative factors, as postulated by Raab). Up to now, no enzymatic influence is known which may cause heart failure, however, ATPase activity is influenced by electrolytes, and some electrolytic effect may be explained by altered ATPase activity

ELECTROLYTES Since the work of Szent-Gyorgyi et al, the influence of electrolytes upon the strength of cardiac contraction has been well known Not enough investigation has been *done on the effect of magnesium,* which is regarded as an antagonist of *calcium* A high blood level of calcium induces ECG changes but has no hemodynamic effect. In hypocalcemia, there is an initial lengthening of ejection time. If there is more marked effect, the ejection time can be considerably abbreviated and it must be assumed that the strength of contraction is diminished in calcium deficiency

Potassium influences contraction strength In the frog heart, the optimal potassium concentration is 4.8 moles Higher or lower concentrations diminish contractility. This can be explained as follows: at rest, the intracellular potassium prevents the union of actomyosin and ATP and the onset of contraction. During excitation, potassium diffuses through the membrane and contraction can take place *The strength of contraction is decisively influenced* by the concentration of potassium within the cells. By a gradual increase in potassium, the tension developed can be decreased in a graded fashion (Szent-Gyorgyi). Clinically, higher or lower levels of potassium lead to an energetico-dynamic type of cardiac failure which is characterized by a *shorter ejection time* accompanied by an early 2d sound The *early 2d sound* indicates weak contraction of the heart muscle, since the ventricular pressure is no longer able to overcome the aortic pressure for a sufficient length of time. Experimentally, little (and clinically, nothing) is known about the influence of the membranes on the strength of contraction Experimentally, Hajdu found certain relations between membrane potential, potassium, and the promptness of contraction; with high membrane-potentials, potassium has to decrease more before the onset of contraction. He postulates that, in infections, there is a membrane damage.

Membrane influences may also be considered the cause of diminished strength of contraction after complete denervation (experimental) and following nervous and hormonal influences in clinical cases (Raab).

THE INFLUENCE OF DIGITALIS ON MYOCARDIAL METABOLISM In spite of extensive investigations, the mode of action of digitalis has not yet been solved. Probably a multiple mechanism is involved Increased breakdown of energy-rich phosphates, influence upon the viscosity of contractile proteins, acceleration of polymerization of actin, and the subsequent increase of contractility of certain ATP-actomyosin preparations, influence the active ionic transport at the cell membrane in regard to inhibition of potassium (Rothlin and Taeschler).

TABLE 18-1 CAUSES OF CARDIAC INSUFFICIENCY

Cause	*Clinical condition*
Impairment of energy production:	
Due to lack of oxygen	Suffocation Hemorrhagic shock Severe coronary occlusion
Due to lack of enzymes	Beriberi
Due to insufficient substrate utilization	Diabetes mellitus
Insufficient energy utilization because of disturbance of:	
Contractile proteins	
Secondary to overload	Congestive heart failure
Primary	Myocardosis (example, hemochromatosis)
Altered ionic activities, chiefly potassium	Energeticodynamic, infectious, toxic
Altered membranes	Autonomic heart failure

VARIOUS FORMS OF CARDIAC INSUFFICIENCY

Theoretically, *heart failure* is mentioned whenever the myocardium is unable to deliver a certain output and to increase it if necessary Practically, in all cases the end-diastolic pressure is increased In a *hemodynamic type of failure*, the cause, in the majority of cases, lies in *abnormal requirements* of the heart muscle (increased pressure in the lesser or greater circulation, valvular damage, and disability of certain areas of heart muscle with resulting additional burden upon the remaining undamaged parts), and, more seldom, in a *lesion of the muscle fibers* themselves (so-called myocardosis in general)

The *pathogenesis* of hemodynamic cardiac insufficiency has been extensively studied during the last few years *Clinically* the effects of the cardiac failure are found more in the periphery than in the heart itself Except for the occasionally observed changes of tension, systole is clinically not shortened, even in the most severe cardiac insufficiency (hemodynamic), the rise of ventricular pressure is sustained for a sufficiently long period of time By recording simultaneous ECG and phonocardiograms, one can note that normally the 2d sound falls at the end of T wave This is different from the results of experimental work, where during increasing load one can observe, first a prolongation, then a marked abbreviation of ejection (Fig 18-6) Clinically, this abbreviation has been observed only in extreme cases, e g, in the terminal stage of hypertensive heart disease, while prolongation is frequently observed in the early stages of hypertension This marked discrepancy between the experimental and clinical observations of the insufficient myocardium has not been studied much until recently In certain clinical observations, this abbreviation of ejection was proved by a premature occurrence of the 2d sound in comparison with the end of T, even though there is a shorter Q-T interval. This can be observed in terminal stages of suffocation. Much more frequently, there is an abbreviated ejection and a prolongation of the Q-T segment (as it was believed to be in the past) or a T-U fusion (according to present knowl-

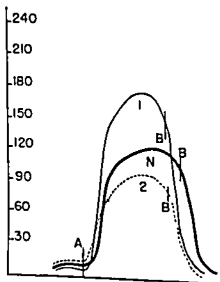


Fig 18-6 Curves representing the ventricular pressure and duration of systole A-B under various conditions N, normal curve; 1, curve after epinephrine, 2, weakness of contraction after chloral hydrate (notice the shortened systole A-B) (After Wiggers. *Circulatory Dynamics*. Grune & Stratton, 1952.)

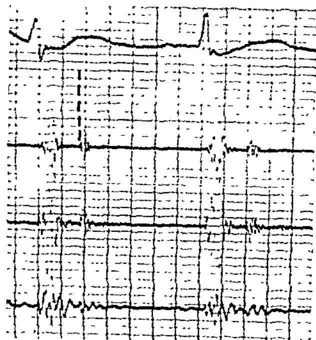


Fig. 18-7. Energeticodynamic cardiac insufficiency with hypopotassemia in diabetic coma. Sixty-five-year-old woman Potassium: 2.13 mEq/L. Blood pressure: 100/60 mm Hg. The mechanical systole is shortened by 0 09 sec as compared to normal.

edge). This then reveals changes, not only of the mechanical manifestations (2d sound) but also of the electrical phenomena (T-U fusion wave) (Fig 18-7) *This abbreviation of the ejection time should be considered as a manifestation of a decreasing contractility of the myocardial fibers because the heart muscle has not sufficient time to overcome the aortic pressure.* The changes of the ECG suggest disturbances in the metabolism of the heart muscle. The simultaneous appearance of *electrocardiographic metabolic disturbances* (T-U fusion wave = *energetic insufficiency*) explains the term *energeticodynamic insufficiency* With the exception of total anoxia (clinically rare), a premature 2d tone is always associated with corresponding electrocardiographic changes, while the ECG changes can be observed even without dynamic insufficiency, apparently, the metabolic disturbances are sometimes not severe enough to cause a marked weakness of the muscle. In such instances, there is an energetic (but not yet a dynamic) insufficiency This association of the typical electrocardiographic and hemodynamic alterations indicates an intimate connection

In most cases, there are disturbances of the electrolyte balance Potassium deficiency, and less frequently *hyperpotassemia,* are the most frequent findings. It is assumed that the electrolytes interfere with the actomyosin-ATP reaction (determining the strength of contraction). However, the degree of disturbance is not proportional to the degree of hypopotassemia. The dynamic disturbances are most severe (premature 2d sound) when hypopotassemia is combined with other severe disturbances in metabolism. *Hypochloremia* sometimes seems to be involved. In other conditions, especially in infectious or toxic conditions, the cause cannot be understood. It is conceivable that there is an influence upon the permeability of membranes regulating the exchanges of ions. Examples might be found in diabetic coma; hepatic coma; severe, prolonged diarrhea, prolonged vomiting; meningeal hemorrhage; liver cirrhosis; nephritis; severe toxic-infectious conditions with myocarditis (diphtheria, poliomyelitis), pneumonia. In rheumatic myocarditis, a prolongation of Q-T is often observed but not a premature 2d sound.

Clinical Manifestations. The characteristic electrocardiographic - phonocardiographic changes are necessary for a diagnosis *When the 2d tone is not synchronous with the end of the T wave,* there is good evidence that such a disturbance is present Normally, there is not more than 0.02 sec between the end of T and the beginning of the 2d tone. For practical purposes, it is not important to know if a U wave is hidden in the ending of the T wave The interval Q–2d sound is determined according to a formula (Hegglin and Holzmann) valid for the normal Q-T interval

$$0.39\sqrt{RR} \pm 0.04 \text{ sec}$$

Absolute abbreviations below the average value of −0.04 sec are rare. Average values of −0.02 sec can already be considered as pathological As the range of values (±0 04 sec) is large, serial examinations are of great importance (Figs. 18-8 and 18-9).

The diagnosis can be, however, *attempted* by using other clinical data. By means of *auscultation,* a trained ear can distinguish the premature 2d tone. The interval between the 1st and the 2d tone then becomes very short, something that old practitioners considered as an ominous prognostic sign. The *2d tone can* become soft. The *pulse* is small. The rate varies. there were cases with severe tachycardia

while others had a normal rate or even bradycardia The *blood pressure* is usually low, but not to such an extent that one can speak of collapse This syndrome, on the other hand, can be observed even in cases of arterial hypertension.

Congestion and *edema* are usually not observed (crepitant rales are occasionally present over the pulmonary bases). The *venous pressure* is not elevated *Circulation times* are abbreviated and become normal after improvement of the pathological condition The *circulatory volume* is decreased and *cardiac output* is also decreased There is nothing known about the intracardiac pressure conditions as no cardiac catheterization has been done in such cases

The prognosis depends upon the underlying disease The cardiac disturbance is reversible by adequate therapy (Fig 18-8). A very premature 2d sound, however, is significant of a poor prognosis

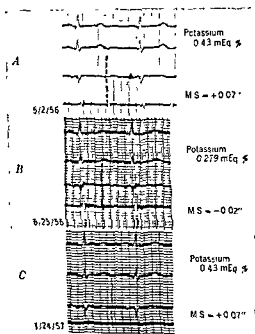


Fig 18 8 Changing length of the mechanical duration of systole in serial examinations (case of interstitial nephritis) A, Normal behavior B T-U-fusion wave as an expression of disturbance of myocardial metabolism (hypopotassemia potassium = 2 79 mEq/L), energetic insufficiency The mechanical systole is shortened only insignificantly by 0 02 sec C, Normalization of the serum potassium and of the electrocardiogram.

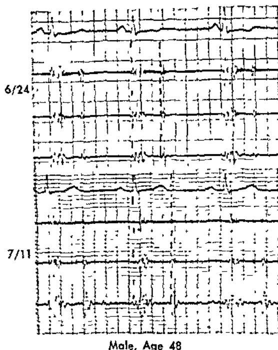


Fig. 18-9. Development of a typical cardiac insufficiency of the energetic-dynamic type in a patient with acute myocarditis and no changes in electrolytes Forty-eight-year-old man The mechanical systole, shortened by 0 08 sec on 6 24, reached the average value on 7/11. During a rate of 75 per minute, the interval Q–2d sound changed from 0 25 to 0 33 sec

I

Causes and clinical picture of paroxysmal pulmonary edema

ALDO A. LUISADA

Paroxysmal pulmonary edema, first described two centuries ago, is still a subject of great interest to clinicians and physiologists At present, acute pulmonary edema is considered by most clinicians to be a manifestation of failure of the left ventricle, the clinical symptoms being due to back-pressure into the blood vessels of the lung. This concept was originally based on the experimental studies of Welch (1878) who reported the development of pulmonary edema in rabbits as a result of interference with the function of the left ventricle. Indeed, the back-pressure concept is not limited solely to acute pulmonary edema but has been extended to the respiratory manifestations of chronic congestive failure as well (Harrison) As experimental and clinical observations on pulmonary edema have accumulated, it has become clear that the validity of the "back-pressure" or "left ventricular failure" theory of acute pulmonary edema can no longer be considered established and that it should be considered, at best, incomplete

As defined by Laennec, "Edema of the lung is the infiltration of serum into the substance of this organ, in such degree as evidently to diminish its permeability to the air, in respiration" While edema of the lungs is initially similar to edema of other organs, the structures surrounding the capillaries are so thin that an immediate outpouring of fluid into the alveolar cavities occurs. In this respect, pulmonary "edema" is followed by pulmonary "exudation" To a more limited extent, fluid also appears in the pleural cavities.

The term "pulmonary edema" carries with it different associations to different specialists to the pediatrician, acute glomerulonephritis or rheumatic carditis; to the surgeon, thoracic or abdominal intervention, to the neurologist, cerebrovascular accident or trauma to the skull, to the cardiologist, hypertension, coronary occlusion, or mitral stenosis.

HISTORY

The history of lung edema is long. Although nearly two centuries have elapsed since the first clinical description, the first experimental researches were performed nearly 100 years ago

The multiplicity of the causes which give rise to attacks of lung edema and the different theories attempting to explain it call attention to the fact that it is one of the most interesting, although still obscure, acute syndromes.

A brief list of the chief studies on the subject will be of some interest.

1752 Maloet, clinical description
1753: Barrère and Albertini, clinical study
1760–1770 van Swieten, Sir Percival Scott; clinical studies.
1819 Laennec, inflammatory lung edema, lung edema in patients with cardiac diseases.

1834· Andral, acute and chronic lung edema

1836 Legendre, inflammatory lung edema during scarlet fever, acute lung edema in patients with nephritis.

1850–1860 Devay, Rilliez, and Barthez, complete description of the clinical picture

1850–1860. Virchow, research on lung edema following fat embolism

1850–1860. Cohnheim and Lichtheim, research on lung edema after intravenous salt solution infusion

1869. Peter, lung edema in pregnant women

1873: Terrillon, lung edema following thoracentesis.

1873 Souin de la Savinière, lung edema during pneumonia.

1877: von Frey, experimental researches on cutting of vagus nerves

1878 Welch, lung edema of the rabbit either by ligature of the aorta or by compression of the left ventricle

1878. S Mayer, lung edema of the rabbit by brain ischemia.

1879 Huchard, clinical study on the relationship between lung edema and aortic lesions.

1880–1896 von Basch, Loewit, Grossmann, Winkler, experimental research on toxic lung edema

1888 Sahli, research on experimental edema by ligature of the aorta and by compression of the left ventricle in the dog.

1892 Alexandrow, experimental research on mechanical lung edema

1897 Huchard and Claude, experimental researches on lung edema caused by epinephrine.

1900. Sticker, clinical study on lung edema

1900 International meeting in Paris on lung edema (von Basch, Teissier, Huchard, Potain)

1901 Teissier and Guinard, experimental research on lung edema

1904 Meltzer, pathophysiology of pulmonary edema.

1906 Joreš, research on neurogenic lung edema.

1908–1912 Josué, Cavina, experimental lung edema caused by epinephrine

1909 Miller and Matthews, experimental lung edema

1912 Barringer, acute lung edema during pregnancy and labor

1910–1912 Lian and Vaquez, complete formation of the theory "lung edema is the result of left ventricular failure"

1913 Kotowschtschikow, research on mechanical and toxic lung edema of the rabbit and dog

1918–1927 Moutier, Antonini and Biancalani, acute lung edema caused by injury to the skull

1923–1933 Gallavardin, Sfloz and Frommel, Doumer, Hess, Schellong, acute lung edema in patients with mitral stenosis

1923–1926 Barry; Anrep and Bulatao; Lambert and Gremels, lung edema in heart-lung preparations

1928. Luisada, experimental research on epinephrine pulmonary edema and on the therapeutic value of narcotics and sedatives.

1929. Luisada, intravenous therapy of clinical pulmonary edema with morphine, chloral, and barbiturates

1929 Glass, Boggian, inhibition of epinephrine pulmonary edema by lesions of the brain or of the sympathetic system

1929 Antoniazzi, lung edema by ligature of the aorta, influence of nervous stimuli and of drugs in its prevention.

1930 Luisada, experimental lung edema caused by cerebral hypertension.

1930–1931. Frugoni (with Melli, Peserico, Luisada), acute lung edema. A report to the Italian Meeting of Internal Medicine, and a monograph

1929–1932 Zdansky, x-ray studies on pulmonary edema

1931–1933 Bsteh; Gernez and Marchandise, clinical studies on lung edema in neurological conditions

1932. Weiser, vagal pneumonia-pulmonary edema

1932 Luisada, criticism of the theory of isolated ventricular failures (monograph).

1931–1933 Hess, clinical studies of pulmonary edema after coronary occlusion

1933 Coelho and associates, lung edema by experimental lesions of the left ventricle on the dog.

1934 Reinhardt, experimental researches on lung edema with microscopic control

1934 S Wassermann, a monographic study on clinical lung edema.

1934 Brunn, luminal inhibition of experimental lung edema

1935 McGinn and White, acute cor pulmonale

1935 Cataldi, pulmonary edema by experimental lesions of the right ventricle

1934–1938 Cataldi, Rubino, studies on dynamic effects of the experimental lesions of either the right or the left ventricle, and of ligature of either coronary artery.

1932–1938 Hochrein and associates, the lung a blood depot, vasomotor changes of the lung vessels

1934–1939 Laubry and Cottet, Manunza, Astuni, Weissmann, lung edema in the diseases of the nervous system and after trauma to the skull.

1936 Moon and Morgan, experimental lung edema during shock

1937 Farber, lung edema by cutting of the vagus nerves.

1938. Barach, positive pressure in the treatment of pulmonary edema.

1939: Jarisch and associates, central lung edema by suboccipital injection of veratrin in animals.

1940–1944: Cournand and associates; Dexter and associates; changes of pulmonary pressures studied by catheterization

1944: Sarnoff et al., spinal anesthesia as treatment of pulmonary edema.

1945. Drinker, monograph on pulmonary edema.

1946· Luisada and Sarnoff, Paroxysmal pulmonary edema consequent to stimulation of cardiovascular receptors

1948: Daniel and Cate, the surgical "wet lung."

1949: Visscher et al., pulmonary edema in animals with increased cranial pressure.

1949: Koenig and Koenig, ammonium chloride pulmonary edema.

1949: Cameron et al., neurogenic pulmonary edema.

1950: McKay, edema of the lung in trauma to the skull. *Hypoglycemic pulmonary edema.*

1950: Luisada, antifoaming agents in experimental pulmonary edema.

1952· Luisada et al, antifoaming agents in clinical pulmonary edema

1952· Lenègre and Scébat, physiopathology of pulmonary edema in the cardiacs.

1952. Reich et al, silicones as antifoaming agents

1952· Sarnoff et al, neurohemodynamic pulmonary edema.

1953: Luisada and Contro, further studies on neurogenic pulmonary edema.

1954. Altschule, monograph on pulmonary edema.

1955. Luisada and Cardi, further studies with antifoaming agents.

1955: Katz et al, pulmonary edema resulting from pulmonary embolisms

1956: Luisada and Cardi, Visscher et al; general reviews on pulmonary edema

1957. Aviado et al., alloxan pulmonary edema.

1957· Aravanis et al, pulmonary reflexes in experimental pulmonary edema.

1957 Polli and Luisada, splenectomy, nephrectomy, and other procedures in experimental pulmonary edema

1958: Symposium on Pulmonary Circulation (Chicago).

TABLE 18-2 MAIN NECROPSY FINDINGS IN 100 UNSELECTED CASES OF PULMONARY EDEMA

Pathology	*No of cases*
Severe coronary disease	34
Congestive failure	32
Carcinoma of various organs (carcinoma of lungs, 15 cases, obstruction of pulmonic veins, 11 cases)	27
Bronchopneumonia	23
Hypertensive heart disease	18
Massive pulmonary embolism	10
Cerebral hemorrhage	9
Cerebral tumor	7
Tuberculosis	6
Liver cirrhosis	6
Fractured skull	3
Multiple fractures (excluding skull)	2

SOURCE From Cameron.

TABLE 18-3. FREQUENCY OF PULMONARY EDEMA IN 500 AUTOPSIES OF SPECIAL CONDITIONS

Pathology	*Total no of cases*	*No showing pulmonary edema*
Hypertensive heart disease (excluding chronic nephritis)	94	81 (86%)
Chronic nephritis	50	37 (74%)
Coronary occlusion	66	45 (68%)
Cerebral hemorrhage	66	44 (67%)
Mitral stenosis	84	55 (65%)
Fractured skull	38	24 (63%)
Multiple fractures (excluding skull)	28	17 (61%)
Pulmonary embolism	74	23 (31%)

SOURCE: From Cameron

CAUSATIVE FACTORS

Paroxysmal pulmonary edema can be encountered in a great variety of conditions, as shown by *necropsy findings* (Tables 18-2, 18-3). A list of the various conditions which may be associated with acute pulmonary edema is presented below. As a large number of clinical cases succumb without pulmonary edema, this disorder is not a "terminal" or "agonal" phenomenon.

A brief review of the most common causes of pulmonary edema in clinical cases follows.

Pulmonary Edema and Arterial Hypertension. This type of pulmonary edema was most common in the past, but is now seen less frequently, partly because of the development of more effective treatments, and partly because other types tend to predominate. *Chronic nephritis with uremia* is frequently accompanied by episodes of edema of the lungs, but sometimes moderate nitrogen retention is the only evidence of renal insufficiency, and there may be little or no *acidosis*. All other forms of hypertension, including essential hypertension and that of coarctation of the aorta, may present pulmonary edema. Patients with *malignant hypertension* have these paroxysmal attacks more commonly than others

Pulmonary Edema and Coronary Heart Disease. The observation that severe coronary occlusion is frequently accompanied by pulmonary edema has led to the belief that minor coronary episodes may also contribute to these attacks. However, no certain proof has been

Clinical Conditions Associated with Acute Pulmonary Edema

I Cardiovascular disease
- *A* Syphilitic heart disease (aortic insufficiency, aortitis; aortic aneurysm)
- *B* Rheumatic heart disease (acute rheumatic carditis; mitral insufficiency; mitral stenosis; aortic insufficiency; aortic stenosis)
- *C.* Coronary heart disease (severe, acute coronary occlusion; minor occlusion plus extensive ischemia or fibrosis of the myocardium)
- *D* [illegible] glomerulo- [illegible]
- *E.* [illegible] patent [illegible]
- *F* [illegible]
- *G* [illegible]
- *H* Congestive failure

II Diseases or lesions of the central nervous system
- *A* Trauma to the skull
- *B* [illegible] tumor)

[illegible]
- *A* Pneumonia, bronchopneumonia (especially influenzal)
- *B* Drowning, strangulation, asphyxia, respiratory obstruction (edema of the glottis, bronchial asthma, foreign bodies)
- *C* Inhalation of irritant or toxic gases (including those used in warfare), respiratory burns
- *D* Following rapid thoracentesis
- *E* Following trauma to the chest
- *F* Following lobectomy

IV Allergy
- *A* Angioneurotic edema, serum sickness, following injection of gold preparations; following inhalation of penicillin aerosol

V [illegible]

VI Surgical and obstetric cases
- *A* During pregnancy or after labor (especially, but not only, in cases with rheumatic heart disease, [illegible]
- *B* [illegible]
- *C* [illegible]

VII Toxic
- *A* Following use or overdose of thiourea derivatives, iodides, muscarine, eserine, Prostigmine, opium, methyl salicylate, acetic and butyric ether, phenylcarbamide

VIII Miscellaneous
- *A* Thyroid crises, beriberi, insulin shock, burns

presented, and the mechanism of production of the edema might be somewhat different from that in hypertensive patients *Cardiogenic shock* caused by coronary occlusion is more frequently associated with pulmonary edema than other types of shock Protracted forms of edema of the lungs are common in coronary heart patients

Pulmonary Edema and Cerebral Diseases. The occurrence of pulmonary edema in cases of meningitis, encephalitis, or brain tumor is relatively common, in children as well as in adults *Cerebrovascular attacks,* including hemorrhage, embolism or thrombosis, and subarachnoid hemorrhage, as well as trauma to the skull, are frequently followed by pulmonary edema Undoubtedly, coronary lesions and preexisting hypertension may be contributing factors in certain cases. However, in others, no evidence of such lesion or disorder can be demonstrated clinically following recovery, or at autopsy.

Manipulation of the Stellate Ganglia. Early in the history of sympathetic surgery for coronary heart disease, acute pulmonary edema was reported to occur during the course of manipulation of the stellate ganglia in about half of the cases (Jonnesco, Danielopolu) More recently, probably as a result of refinement of technique, this has become uncommon.

Pulmonary Edema and Pulmonary Heart Disease. Contrary to current opinion, this as-

sociation is far from rare. Pulmonary edema may follow *pulmonary embolism*. Occlusion of one stem of the pulmonary artery causes increased flow in the other, and this may favor high capillary pressure in one lung Even occlusion of smaller branches may cause diffuse, bilateral edema, a fact which has led to numerous speculations on the possibility of either diffuse reflexes acting on the pulmonary vessels or the liberation of substances increasing the permeability of the capillaries.

Acute pulmonary edema may develop even in *chronic cor pulmonale* with right ventricular hypertrophy and pulmonary hypertension. It should be kept in mind that chronic cor pulmonale (or pulmonary heart disease) is the result of a long-lasting, usually diffuse, lesion of the lungs.

Several forms should be differentiated:

1. The form due to *increased flow* plus vasoconstriction or minor arteriosclerotic lesions of the arterioles This form, called "hyperkinetic" by Wood, is typical of congenital shunts.

2. The form caused by *obstructive lesions of the pulmonary arterioles* (primary pulmonary arteriosclerosis, secondary arteriosclerosis of mitral stenosis, and syphilitic arteritis). This leads to pulmonary arterial hypertension and right ventricular strain while no impairment of the gas exchange between pulmonary capillaries and alveoli takes place. There is *no* decrease in oxygen saturation of the arterial blood and *no* polycythemia until the late stages.

3 The form caused by *obliterative lesions of the pulmonary parenchyma* (pulmonary emphysema, pulmonary fibrosis which may follow extensive pneumonia, bronchopneumonia, pulmonary tuberculosis, or bronchiectasis; diffuse but slowly growing cancer of the lungs, and multiple and repeated pulmonary infarctions) This leads to pulmonary hypertension through destruction of the capillaries and is followed by a decrease in the oxygen saturation of the arterial blood (hypoxia) and polycythemia.

4. The form caused by *impairment of respiration* due to kyphoscoliosis or other *deformity of the chest*. It may cause hypoxia

5. The form caused by an *arteriovenous shunt* due to one or more fistulas of the lung. The bypassing of the capillaries may cause hypoxia

For a long time, it was denied that edema of the pulmonary parenchyma might occur in chronic cor pulmonale because any obstruction of the small vessels, while increasing the pressure in the main pulmonary artery and the right ventricle, would also decrease the pressure in the capillaries, the most important site in regard to the formation of edema. However, as shown above, not all forms of chronic cor pulmonale are due to obstruction of capillary flow or destruction of capillaries. Moreover, it should be kept in mind that pulmonary fibrosis frequently predominates in certain areas of the lungs while other areas are intact. It is likely that vascular obstruction, or destruction of a number of portions of the vascular tree, favors pulmonary edema of the intact areas. It is *known that one-half of the pulmonary vessels* can carry the entire flow of the lesser circulation without any increase in pressure. However, this is obtained through distention of the normal vessels, which in itself predisposes to edema. Whenever an increase of venous return takes place in patients with such a distention, the already distended (normal) vessels are taxed beyond physiologic limits, and transudation is more likely to occur in them

Sudden pulmonary edema has been observed in patients with *deformity of the chest* ("pulmonocardiac failure" of Chapman et al). The importance of further lowering of oxygen saturation in such cases cannot be overemphasized *Hypoxia*, as first shown by Drinker, favors pulmonary edema, both through increase of permeability and through increase of pressure in the pulmonary capillaries

Whenever other causes of pulmonary edema are present, *this condition may* also develop in chronic cor pulmonale. This particularly applies to systemic hypertension and coronary heart disease.

Pulmonary Edema in Trauma to the Chest. This syndrome, called by surgeons "traumatic wet lung," has been the object of considerable speculation, and is of particular *interest* because it spreads from the damaged to the intact areas of the lungs.

Thoracentesis. Although the older literature contains references to pulmonary edema following thoracentesis, it is only occasionally seen now. It is likely that refinements in technique (slow decompression) are responsible for the disappearance of this complication

Drowning. The fluid found in the lungs of drowned persons and *animals* has a high protein content (Biondi; Melli; Farber, 1937b). This must result from the transudation of serum into the alveoli, i e., pulmonary edema

Uremia. Acute pulmonary edema is frequently observed during the course of chronic uremia It is especially common in patients who are receiving intravenous infusions of fluid, even at rates as low as 4 to 10 drops/min This is usually ascribed to failure of the left ventricle although positive evidence in that regard is lacking. Moreover, these patients show a predominant dilatation of the right atrium and ventricle. Blood dilution with decreased osmotic pressure of the plasma is likely to be another factor.

Allergy. The possibility of the occurrence of angioneurotic edema of the lungs cannot be ruled out. In a comprehensive statistical study of allergic patients, Frugoni saw no proved case of this disorder, although in many cases an allergic origin was claimed by various authors, in some instances rather convincingly (Sticker). If allergic pulmonary edema does occur, it is clear that there is nothing to suggest that left ventricular failure is implicated Constriction of pulmonary venules, typical in rodents, fairly well developed in carnivores, could be a factor in man.

Pulmonary Edema and Shock. Shock is frequently associated with pulmonary edema It is not known whether shock itself causes pulmonary edema or whether both shock and pulmonary edema result from a common cause Experimental *anaphylactic shock* is usually accompanied by pulmonary edema, as is the episode of *cardiogenic shock* in clinical cases As the former is primarily a vascular disorder while, in the latter, the low blood pressure is due to a cardiac disturbance, it is likely that an upset of the normal hydrostatic/osmotic balance of the capillaries is a factor whenever too severe and prolonged hypotension takes place

Thyroid Crises. Acute pulmonary edema may terminate the course of thyroid crises Its occurrence is usually explained on the basis of left ventricular failure due to increased cardiac output, hypertension, and impaired nutrition of the myocardium.

Beriberi. This disease frequently results in acute pulmonary edema. Since beriberi heart is usually considered due to right heart failure, it is evident that failure of the left ventricle cannot be implicated, neuritis of the vagus has been offered as a possible, though unconvincing, explanation for this type of pulmonary edema. Direct effect on the capillary wall is, of course, a possibility

Stimulation of Hollow Viscera. The older literature contains many instances of pulmonary edema associated with distention of some abdominal organ, usually the stomach. More recent cases are those of Hochrein (stomach) and Vigi (esophagus). These cases are hard to evaluate, either because of inadequate study or incompletely presented data, or because the patients were old persons with coronary sclerosis, valvular defects, or hypertension It is probable that rapid distention of a hollow viscus does not by itself cause pulmonary edema, though the importance of nervous reflexes is suggested. In rare instances, sudden emptying of a distended bladder in patients with prostatic obstruction may apparently result in the development of acute pulmonary edema (Frugoni) This phenomenon is difficult to evaluate, since often the patients in whom it occurs have marked coronary sclerosis, hypertension, or both.

Pregnancy. A number of authors during the last century stressed the relationship between pregnancy and pulmonary edema in some patients Since patients developing this complication have valvular heart disease or hypertension associated with toxemia, this type of pulmonary edema is best considered together with that due to heart disease. Increased blood volume is, however, an additional factor.

Pulmonary Edema in Mitral Stenosis. The occurrence of pulmonary edema in cases with a persistent block *before* the left ventricle contradicted the established theory attributing these episodes to acute left ventricular failure It is only in recent years that an adequate dynamic explanation has been found. Patients with mitral stenosis occasionally cough up large amounts of pure blood. This syndrome, called *"pulmonary apoplexy,"* is closely related to pulmonary edema, and has a similar, though not identical, mechanism.

Pulmonary Edema and Infections. Pulmonary edema and bacterial pneumonia may be closely interrelated because pneumonia may predispose to pulmonary edema (infectious pulmonary edema) and vice versa (infected pulmonary edema) Furthermore, either of these conditions may simulate the other. Many other febrile diseases may be complicated by pulmonary edema, partly through

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repercussions of inflammatory lesions of the heart, lungs, or brain, and partly through possible overload of the circulation caused by therapeutic intravenous infusions. Unexplained edema of the lungs may also develop during the chill phase of a febrile reaction. Acute infectious pulmonary edema was discussed (in this and other diseases) by Logre, and more recently, by Robin and Thomas.

Pneumonitis. Viral pneumonitis, especially *influenzal*, may cause pulmonary edema, even in young patients in whom there is no evidence of heart disease. During epidemics of influenza, acute pulmonary edema is a not infrequent cause of death.

THE CLINICAL EPISODE

An attack of pulmonary edema may occur at any time of the day or night. Precordial oppression or pain, restlessness, weakness, and dry nonproductive cough, may precede the attack If this occurs at night, a nightmare frequently precedes the paroxysm. Respiration becomes difficult and labored, and is usually accelerated The patient is obliged to sit up, and may lean forward Within a few minutes, gurgling sounds can be heard, and the patient repeatedly emits a white, yellowish, or pink *frothy sputum*. This may vary from a few bubbles to enormous amounts (as much as 2,000 to 3,000 ml of foam within 1 to 2 hr). Cold, clammy extremities, paroxysms of suffocation, and vomiting may occur.

In most cases connected with coronary occlusion, pulmonary embolism, or allergic shock, the pulse is rapid and small (and may be irregular), and the blood pressure drops gradually, sometimes reaching shock level Some cases with a rheumatic mitral lesion also experience a drop in blood pressure.

Other cases, and particularly those occurring in hypertensive or syphilitic heart disease, and those connected with a cerebrovascular attack, present a full pulse and a blood pressure which is high, and sometimes higher than before the attack.

Physical examination reveals a high, tympanic percussion sound over the lung fields and innumerable moist rales over the entire chest, from the soft rales arising in the small bronchi to the gurgling sounds created by the foam in the trachea.

The *temperature* is usually normal during the attack, except in inflammatory edema, but may rise soon afterward because of reabsorption of altered proteins from the lungs.

The *sputum* has a chemical composition similar to the fluid of angioneurotic edema or allergic coryza and to the inflammatory effusions of large serosal cavities. This is true, not only of clinical episodes, but also of experimentally induced attacks.

Catheterization of the right heart in clinical cases has revealed that pulmonary arterial pressure is severely increased, and that pulmonary artery wedge pressure may reach from 32 to 45 mm Hg during the attack (Lenègre and Scébat).

VARIETIES

Extreme difference can occur in the clinical picture of pulmonary edema according to the severity, extension, duration, and clinical picture.

Extension. Pulmonary edema is usually bilateral and, contrary to common belief, it usually starts in the hilar regions, then diffusing to the rest of the lungs. Certain forms of moderate severity may not involve all the parenchyma of both lungs. *Unilateral pulmonary edema* is possible. It is usually favored by decubitus, infection of one lung, or neurological phenomena The author has observed one case where it was connected with a small abscess of one lung plus a contralateral cerebral embolism (autopsy confirmed these facts).

Other cases were described by Stricker and by Teissier.

Duration. Certain episodes are *fulminating*, so that the occurrence of edema of the lung is only an autopsy finding Most serious cases last for 20 min to 2 to 3 hr and thus give ample time for treatment. These are the *acute cases* A special variety has been called *protracted edema* (Goldmann and Luisada) It occurs following either a myocardial infarct or a cerebrovascular accident. It starts as an acute form and then continues for 6 to 24 hr, and even longer. *Chronic pulmonary edema* obviously is not described here.

Severity. The severity of an attack is not always proportional to its duration Severe episodes may disappear after 15 to 30 min while moderate episodes may be prolonged and last several hours.

Clinical Picture. One symptom or sign may predominate. Precordial pain or oppression, cough, asphyxia (bronchoplegic form), un-

consciousness, abundance of expectoration, or hemorrhagic sputum, can predominate. Precordial pain is typical of myocardial infarction; loss of consciousness is common in cerebral episodes; bloody sputum is typical of mitral stenosis.

Wheezing respiration is uncommon but may occur Then, expectoration is usually moderate while dyspnea is extremely severe.

THE TWO MAIN TYPES OF PULMONARY EDEMA

While different signs have led to the recognition of various clinical pictures of pulmonary edema, two groups deserve distinction because of the different effect that treatment exerts on the clinical picture and on the final course.

Patients of the *first group*, who seem to be the most numerous, present evidence of increased blood pressure, rapid circulation, increased cardiac output, and extreme rise in pulmonary arterial pressure This group includes patients with hypertensive heart disease; patients with syphilitic or rheumatic heart disease and aortic insufficiency, some instances of cerebrovascular accidents, mitral insufficiency, or minor coronary episodes, and patients treated with overabundant venous infusions or transfusions. It is apparent that any method which succeeds in decreasing venous return to the right heart will be helpful in this type of edema

Patients of the *second group*, less numerous but tending to increase, present either no change or a drop in blood pressure, decreased cardiac output, and a more moderate rise in pulmonary arterial pressure (some cases may even have a normal pulmonary arterial pressure) This group includes patients with massive myocardial infarct, some instances of severe mitral or aortic block, some patients who have inhaled toxic gases, some instances of cerebrovascular accident, and some patients with toxic, rheumatic, or bacterial myocarditis While a reduction in venous return may be useful in these patients, it also carries with it the danger of precipitating shock

CARDIOVASCULAR DYNAMICS IN CLINICAL CASES

It is difficult to obtain data on the cardiovascular dynamics during acute pulmonary edema. The attacks are frequently of short duration or, if sufficiently prolonged to permit accurate observations, make the patient extremely uncomfortable and even desperately ill. Nevertheless, valuable data can be obtained from observations made in milder forms of paroxysmal cardiac dyspnea, which are closely related to the syndrome of acute pulmonary edema itself, or from patients who experienced pulmonary edema during cardiac catheterization. The latter has been the object of a study by Lenègre and Scébat.

Measurements of *pulse rate* and *blood pressure* are easily obtained during attacks of pulmonary edema or paroxysmal dyspnea. In most instances, both are elevated during the attack but blood pressure may be low or follow a slowly decreasing course.

Venous pressure has been measured by Weiss and Robb and by Altschule in patients with paroxysmal dyspnea, and a considerable increase was found in some. Altschule suggested that this was due to a rise in intrapleural pressure associated with loss of elasticity and distensibility of the lungs and with increased respiratory efforts. Altschule also advanced the hypothesis that this phenomenon might be important in terminating some attacks, the rise in intrapleural pressure impounding blood in the peripheral veins in a manner similar to tourniquets on the extremities In shock associated with pulmonary edema, the veins are collapsed and the venous pressure is very low.

Studies of the *vital capacity* by Weiss and Robb revealed a considerable decrease during attacks of paroxysmal dyspnea The pulmonary circulation time is also prolonged and the arterial oxygen saturation decreases. These observations explain the dyspnea observed during the attacks.

Measurements of the *cardiac output* during paroxysmal dyspnea are few Eppinger and coworkers made such a study but the method used is now discredited. Lauter, using the Fick principle and cardiac puncture, found (in three cases) a diminished blood flow through the lungs, i e., a decreased output of the right ventricle, during attacks. Weiss and Robb used a dye method to measure the output of the left ventricle This method must be considered far from being satisfactory. However, in a large series of cases, they found low or normal cardiac outputs during paroxysmal dyspnea.

Lenègre and Scébat (1952) measured the

pulmonary arterial pressure and the pulmonary wedge pressure in 13 cases of pulmonary edema (two of them preceding catheterization). The pulmonary wedge pressure rose in all cases reaching from 35 to 45 mm Hg. At the same time, the pulmonary arterial pressure rose by about 30 to 50 per cent. These data were accepted as indicating a consistent rise of pulmonary capillary pressure above the level of the colloid osmotic pressure of the blood. The foregoing figures are similar to those of Gorlin et al. (1951), who found pressures of 32 to 54 mm Hg during episodes of pulmonary edema in mitral stenosis.

Roentgenology in acute pulmonary edema

FELIX G. FLEISCHNER

Acute pulmonary edema is set apart clinically by its paroxysmal character It may occur as a deterioration of pulmonary congestion More often, however, it occurs without preceding congestion In many instances, acute pulmonary edema is characterized also by a particular roentgenographic appearance, and this fact justifies a special discussion

As roentgenographic examination of the chest is increasingly used in more acute conditions, perihilar densities of a particular shape in pulmonary edema were observed by early authors (Day et al, Roubier and Planchu, Zdansky, and others). The term *butterfly density* was introduced by Nessa and Rigler, *batwing shadow*, by Hodson; *central*

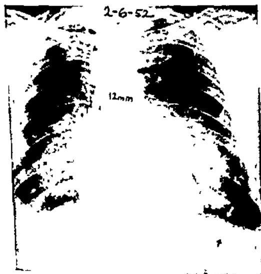


Fig 18-10 Man, aged 49 years Acute central pulmonary edema (type 1) This patient with a past myocardial infarct suffered from an upper respiratory infection while in a stage of borderline compensation. Bilateral central consolidation is seen, leaving the outer two-thirds of the lung fields clear There are also bilateral pleural effusion and a thick left "diaphragm" (arrows) revealing fluid between lung and diaphragm.



Fig. 18-11. The patient recovered with bed rest, antibiotics, and digitalis, losing 15 lb through diuresis The hilar vessels are still engorged, but otherwise the lung fields are clear. Notice the thin left "diaphragm" The azygos vein, previously 12 mm wide, now measures only 6 mm.

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with uremia are frequently accompanied by episodes of pulmonary edema is probably due to arterial hypertension and left-sided failure (Luisada), possibly also to a generalized capillary damage in glomerulonephritis.

The known facts on the causes and pathology of pulmonary edema do not explain this particular central distribution of edema and the sparing of the periphery Structural or physiologic differences between the central and peripheral portions of the lung had to be sought (Kerley), and several attempts in this direction have been made

Marchand showed that rich connective tissue extended from the mediastinum along bronchi and vessels as far as the third or fourth division. He thought that pulmonary transudate would accumulate along these paths. By experiments with injection of opaque media on cadavers he produced "butterfly shadows."

Herrnheiser and Hinson confirmed (by the use of the whole section technique of Gough and Wentworth) that the *central arrangement* of edema exists also in the pathological specimen, that, in anthracotic lungs, there is a different distribution of coal dust in the central and peripheral portions, suggesting a difference of lymph drainage in these two portions. They subdivided the lung into root, medullary, and cortical parts of the lobes, according to anatomical differences The vessels branch in different fashion In the *cortical, peripheral portion*, they divide proportionately, in the *medullary, central portion*, mostly in a disproportionate fashion. It is assumed that this disproportionate confluence of veins and lymphatics interferes with proper drainage.

The concept that not all arteries are permanently perfused but that individual arteries and even whole areas are temporarily shut down as "block-arteries" (Sperrarterien) has been revived. Prichard et al have shown by angiography that sometimes the vessels in the periphery of the lung do not fill. Zdansky emphasized the effect of the ventilatory excursion upon the blood circulation and lymph drainage (Tendeloo; Drinker and Warren). Under the conditions prevailing during pulmonary congestion, the blood velocity is decreased causing increased transudation in areas of restricted ventilation, and the lymph current is slowed down causing reduced resorption. The central portions of pulmonary parenchyma wedged in the angles between the bigger vascular and bronchial trunks undergo apparently less ventilatory play. In the case of circulatory imbalance, transudate would be readily accumulated there, while the cortical portions, undergoing wider ventilatory excursions and better lymph drainage, would be kept dry.

These anatomicophysiologic factors, individually or together, apparently come into play under the sudden impact of circulatory disturbances of a certain degree. Thus central edema is not present, or it may be obscured, when chronic congestion preexists, and it is not seen in severe massive edema which drowns the lung all the way out to the pleura These factors satisfactorily explain the otherwise enigmatic roentgenographic appearance of acute central pulmonary edema.

edema by Gould and Torrance. (Fig. 18-10.)

Two representative subgroups may be described. In both instances the changes are rather symmetrical. In one type there are rather dense, almost homogeneous shadows occupying and surrounding the hilar regions, extending not more than half way to the periphery (Fig. 18-11). The lateral contours of these shadows are rather fuzzy. The remaining wide peripheral zone, apex, and lateral and basal portions of the lung field show normal or almost normal radiance The other type is even more surprising (Fig 18-12). The shadow is usually less dense, more of a blotchy-confluent type. It extends further toward the periphery but does not reach the chest wall. Again, the apical, lateral, and basal zones remain clear, this time for a width of only 2 to 4 cm In these instances, the edge of the zone of edema is often amazingly well contrasted against the clear peripheral zone. In the posteroanterior view, there is usually a waistlike indentation corresponding to the lesser interlobar fissure on the right, with corresponding interlobar indentations in the lateral view. In both types, a small or medium-sized pleural effusion is usually present. This represents the most characteristic, fully developed picture. Complications may modify it. This is true in the case of preexisting disease, e g, tuberculosis, fibrosis, and bullous emphysema, and in that of concurrent or collateral disease, such as pneumonia or infarcts. The early beginning may present less characteristic pictures, only faint, flecky haziness in the central lung fields. The clearance may be rapid; it usually begins at the periphery. In other instances it may proceed in the opposite direction, leaving mottled or ribbonlike shadows for a number of days; the nature of these shadows could not be guessed out of context with the clinical history and with previous or later roentgenograms.



Fig. 18-12. Man, aged 46 years Acute pulmonary edema (type 2) Classical "butterfly shadows" This patient had repeated myocardial infarcts; most episodes were accompanied by acute pulmonary edema of this type. There was no nitrogen retention and, at necropsy, no renal disease was found. On the left, the dense central shadow stands out, well defined, against the clear surrounding cortex of the lung. On the right, the waist indentation, caused by the horizontal fissure, partially blurs this identical arrangement. Here again, pleural effusion is found between lung and diaphragm, and is readily recognized on the left (arrow).

Edema fluid is found in the interstitial spaces and also in the alveoli and bronchioles, this may vary from a clear transudate to a cellular, albuminous, sticky or hemorrhagic exudate In instances of recurrent edema, hyaline membranes often line the alveoli and plug bronchioles (Bass et al.). None of these observations, however, have been found to be related to a specific causation or particular distribution of the edema.

The unusual butterfly arrangement of the edema, however, stimulated speculation as to its cause This was enhanced by the complexity of the entire problem, by the fact that this particular distribution had never before attracted attention, and by the fact that some of the earlier observations had been made on patients with renal disease Thus, from "pulmonary edema in patients with cardiorenal azotemia" (Roubier and Planchu), developed "pulmonary manifestations of azotemia" (Rendich), to "uremic edema" (Doniach). Soon, however, it became clear that some renal patients with a low nonprotein nitrogen had edema, that the majority of uremic patients do not have pulmonary edema, and that the same butterfly edema is seen much more commonly in nonrenal patients without uremia. Furthermore, no apparent relation between nitrogen retention and pulmonary edema is known (Altschule). That acute and chronic nephritis

quently caused pulmonary edema in the rabbit. Welch (1878) performed similar experiments in rabbits, with the exceptions that the ligature was placed distad to the left subclavian artery and that two of the three great vessels coming off the arch were also tied off; pulmonary edema occurred in these animals. These results could not, however, be obtained in dogs by Sahli, and appeared only in some experiments of Kotowschtschikow. More recently Antoniazzi repeated Welch's experiments in rabbits and only occasionally obtained pulmonary edema, unless the aorta was ligated *without opening* the thorax and without anesthesia. He further observed that previous injection of anesthetics or stellate ganglionectomy prevented pulmonary edema

Sarnoff (1958) has repeated Welch's experi- [illegible] that a dramatic venocon- [illegible] by low pressure in the aorta below the ligature. Such venoconstriction obviously tends to shift a large mass of blood towards the lungs.

INTERFERENCE WITH LEFT VENTRICULAR FUNCTION

By means of manual compression and the use of clamps, Welch produced pulmonary edema in rabbits. Similar experiments were repeated by Loewit, Alexandrow, Sahli, and Kotowschtschikow with inconsistent results in rabbits and rare positive results in dogs. The last two authors named concluded that Welch's results represented agonal changes.

Montanari improved the technique, cutting down in rabbits the size of the left ventricle in contact with the circulation by means of sutures His animals survived without respiratory difficulty unless more than two-thirds of the ventricle was excluded, in this case the animals died rapidly, only rarely showing pulmonary edema A different approach was that of Coelho and Rocheta These authors injected silver nitrate or alcohol into the wall of the left ventricle in dogs, causing pulmonary edema in a large percentage of animals. The significance of these striking findings was, however, put in question by the author's coworker, Cataldi, who obtained the same results (with slightly lower percentage) by injecting the irritating substances into the right ventricle. Cataldi found hypertension of the pulmonary artery and decrease of systemic arterial pressure in animals with this form of pulmonary edema, *irrespective of whether* the pulmonary edema was due to a right or left ventricular lesion.

Attempts were made by Cataldi and by Rubino (in the author's laboratory) to precipitate pulmonary edema in the dog by ligating either the right or left coronary artery, with inconsistent results. (This was due partly to the necessary opening of the chest and positive-pressure respiration, and partly to the effects of anesthesia.) The effect on the cardiovascular dynamics of ligation of either artery was the same, i e, there was a slow decrease in pressure in both pulmonary artery and aorta.

OBSTRUCTION OF PULMONARY VEINS

Attempts have been made to induce pulmonary edema mechanically by obstructing the pulmonary veins. Welch claimed to have observed its occurrence in his experiments on rabbits but Lowit and Antoniazzi could not confirm his findings. Altschule used a somewhat different approach to the same problem. He introduced a balloon into the left atrium through the auricular appendage and connected it to a rubber tube running out through the chest wall Inflation of the atrial balloon failed to produce pulmonary edema even though inflation lasted in some experiments until the animal died, hours later. However, it is true that pulmonary vein occlusion causes pulmonary venous hypertension, as proven by Denolin et al. (1957).

INJECTION OF EPINEPHRINE

It has been known for many years that intraveneous injection of epinephrine in rabbits induces pulmonary edema (Huchard and Claude; Josué, Cavina; Meltzer; Auer and Gates). Since pulmonary edema can be induced in this manner only in rabbits and other small laboratory animals, it is disputable if this phenomenon can be related to the clinical syndrome in man. It is, however, a useful method for inducing pulmonary edema in large groups of animals so as to study the pathological physiology of the process as well as the effects of therapy. The observations of the author, confirmed by Glass, Boggian, and Reinhardt, revealed that sedatives and narcotics (even when they do not induce anes-

I

Experimental pulmonary edema

ALDO A. LUISADA

Several methods have been employed for the experimental production of pulmonary edema. Indirect determinants are listed below.

HEART-LUNG PREPARATION

The earliest observations by Starling and coworkers on the heart-lung preparation recorded the spontaneous occurrence of pulmonary edema in such preparations. Evans pointed out that this phenomenon occurred much more frequently and rapidly in cat than in dog preparations Matsuoka studied the factors responsible for its occurrence and found that increased cardiac work was not a cause but that prolonged duration of the experiments "and general condition of the animal and the operation" were to be implicated He did, however, note the fact that increased pressure and passive dilatation in the pulmonary circuit favored the development of edema. Barry, Lambert and Gremels, and Newton concluded that the chief factor responsible for pulmonary edema in the heart-lung preparation was some change in the composition of the perfusing blood. Indeed, Lambert and Gremels described degenerative changes in the pulmonary vascular endothelium due to the action of this hypothetical toxin. Raising the arterial resistance, according to Matsuoka and Barry, favored the appearance of edema, and Newton reported that obstructing the outflow from the lungs also favored it. Barry, however, found that venous obstruction caused only congestion unless the blood were greatly diluted, under which circumstances edema might develop Anrep and Bulatao reported pulmonary edema when either ventricle failed.

INDIRECT DETERMINANTS OF EXPERIMENTAL PULMONARY EDEMA *

[illegible]

4 Compression or occlusion of left atrium
5 Valvular defects aortic insufficiency, mitral in-
[illegible]

B [illegible]
C Arterial hypotension, shock, hemorrhage
D Embolism

II Alterations of the central nervous system
A Brain lesions compression or stimulation

III Alterations of the peripheral nervous system
A Vagotomy
B Vagotomy with tracheotomy
C Faradic stimulation of lung root

IV Alterations of the respiratory system
A Airway obstruction inspiratory, expiratory, inspiratory and expiratory
B Hypoxia with heart overload or failure
C Respiratory burns and heat
D Drowning
E Intratracheal fluids
F Chest wounds
G Blast

V [illegible]
[illegible] amine), picrotoxin, nicotine
B Lung-irritant gases, oxygen poisoning
C Other agents alloxan, ammonium ion, thiourea compounds, methylene violet, methylene blue, methyl salicylate; acetic, sulfuric, and butyric ether, acetic ether and iodide solution, amyl salicylic ether, iodine and sodium iodide solution, iodoacetamide, bile and bile salts, urethane, carbon monoxide, carbon dioxide, barbiturates
D Metabolic effects alkalosis, hypoglycemia

VI Miscellaneous
A Hyperthermia, sensitivity phenomena mechanical irritation of the bronchus

* Pulmonary edema has been induced by the methods indicated in each of the subheads

SOURCE From Visscher et al., 1956

INCREASED STRAIN ON THE LEFT VENTRICLE

Friedlander (1873) found that ligating the aorta proximal to the innominate artery fre-

quently caused pulmonary edema in the rabbit. Welch (1878) performed similar experiments in rabbits, with the exceptions that the ligature was placed distad to the left subclavian artery and that two of the three great vessels coming off the arch were also tied off; pulmonary edema occurred in these animals. These results could not, however, be obtained in dogs by Sahli, and appeared only in some experiments of Kotowschtschikow. More recently Antoniazzi repeated Welch's experiments in rabbits and only occasionally obtained pulmonary edema, unless the aorta was ligated without opening the thorax and without anesthesia. He further observed that previous injection of anesthetics or stellate ganglionectomy prevented pulmonary edema.

Sarnoff (1958) has repeated Welch's experiments and proved that a dramatic venoconstriction follows the ligation of the aorta. This was considered as a reflex phenomenon caused by low pressure in the aorta below the ligature. Such venoconstriction obviously tends to shift a large mass of blood towards the lungs

INTERFERENCE WITH LEFT VENTRICULAR FUNCTION

By means of manual compression and the use of clamps, Welch produced pulmonary edema in rabbits Similar experiments were repeated by Loewit, Alexandrow, Sahli, and Kotowschtschikow with *inconsistent* results in rabbits and rare positive results in dogs. The last two authors named concluded that Welch's results represented agonal changes

Montanari improved the technique, cutting down in rabbits the size of the left ventricle in contact with the circulation by means of sutures. His animals survived without respiratory difficulty unless more than two-thirds of the ventricle was excluded, in this case the animals died rapidly, only rarely showing pulmonary edema. A different approach was that of Coelho and Rocheta These authors injected silver nitrate or alcohol into the wall of the left ventricle in dogs, causing pulmonary edema in a large percentage of animals. The significance of these striking findings was, however, put in question by the author's coworker, Cataldi, who obtained the same results (with slightly lower percentage) by injecting the irritating substances into the right ventricle Cataldi found hypertension of the pulmonary artery and decrease of systemic arterial pressure in animals with this form of pulmonary edema, *irrespective of* whether the pulmonary edema was due to a right or left ventricular lesion.

Attempts were made by *Cataldi and by* Rubino (in the author's laboratory) to precipitate pulmonary edema in the dog by ligating either the right or left coronary artery, with inconsistent results. (This was due partly to the necessary opening of the chest and positive-pressure respiration, and partly to the effects of anesthesia.) The effect on the cardiovascular dynamics of ligation of either artery was the same; i.e., there was a slow decrease in pressure in both pulmonary artery and aorta.

OBSTRUCTION OF PULMONARY VEINS

Attempts have been made to induce pulmonary edema mechanically by obstructing the pulmonary veins. Welch claimed to have observed its occurrence in his experiments on rabbits but Lowit and Antoniazzi could not confirm his findings. Altschule used a somewhat different approach to the same problem. He introduced a balloon into the left atrium through the auricular appendage and connected it to a rubber tube running out through *the chest* wall. Inflation of the atrial balloon failed to produce pulmonary edema even though inflation lasted in some experiments *until the animal died, hours later However, it* is true that pulmonary vein occlusion causes *pulmonary venous hypertension*, as proven by Denolin et al (1957).

INJECTION OF EPINEPHRINE

It *has been known for many years that* intravenous injection of epinephrine in rabbits induces pulmonary edema (Huchard and Claude, *Josué*, Cavina, Meltzer, Auer and Gates). Since pulmonary edema can be induced in this manner only in rabbits and *other small laboratory animals*, it is disputable if this phenomenon can be related to the clinical syndrome in man. It is, however, a useful *method for inducing* pulmonary edema in large groups of animals so as to study the pathological physiology of the process as well as the *effects of therapy The* observations of the author, confirmed by Glass, Boggian, and Reinhardt, revealed that sedatives and narcotics (*even when* they do not induce anes-

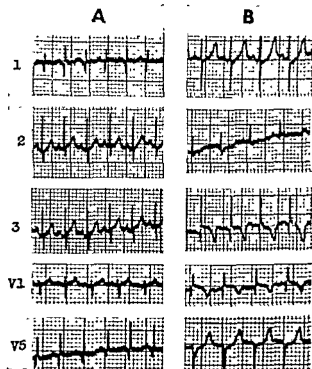


Fig. 18-13. Rabbit. Experimental attack of acute pulmonary edema A. Before injection of epinephrine. Five minutes later, a pattern of left ventricular "strain" had appeared. B Ten minutes after the injection and during pulmonary edema: right ventricular "strain"

thesia), diminish or prevent the edema of the lungs, while respiratory stimulants aggravate it. Luisada (1928b), Glass (1929), and Boggian (1929) showed that cutting all communications between the brain and the periphery prevents epinephrine pulmonary edema, and that previous one-sided sympathectomy, damage to the corpora quadrigemina, or bilateral stellate ganglionectomy also prevent its occurrence.

This method was later used by the author (1950) for evaluation of antifoaming therapy, and by Polli and Luisada (1957) for study of the effects of splenectomy, nephrectomy, and endocrine actions on pulmonary edema. The study of splenectomy extended older studies made by Tremonti (1930a)

A rabbit with acute pulmonary edema caused by epinephrine presents impressive changes of the electrocardiogram (Fig. 18-13) In the first stage, the pattern of *left ventricular "strain"* can be noted, obviously caused by the extreme systemic hypertension However, after a few minutes, this pattern is substituted by that of *right ventricular "strain,"* which is probably the result of the pulmonary edema (Fig 18-13B).

LEFT VENTRICULAR STRAIN

Aortic insufficiency was caused in the dog by cutting one of the leaflets of the aortic valve (Paine et al, 1952). The strain of the left ventricle was further increased by intravenous injection of epinephrine, central nervous system stimulation, or unilateral nephrectomy plus contralateral narrowing of the renal artery, leading to pulmonary edema.

INTRAVENOUS INFUSIONS

Since the studies of Cohnheim and Lichtheim, attempts have been made to induce pulmonary edema by means of injections of salt solutions of various concentration. These authors could not induce it regularly with large amounts of normal saline. Hallion and Carion claimed to produce edema of the lungs regularly with intravenous infusions of hypertonic saline solution, but Melli and Tasso could not confirm these findings. Warthin failed to induce pulmonary edema in dogs with intravenous injections of large amounts of isotonic saline solution. On the other hand, following bilateral vagotomy, edema of the lungs can be precipitated regularly by means of intravenous infusions (Kraus; Brunn; Farber).

Luisada and Sarnoff (1946) succeeded in obtaining pulmonary edema in the dog by very large, rapid intravenous infusions of either saline solution or plasma. They also showed that rapid *intracarotid* infusion toward the brain achieves the same result but with smaller doses and more consistently. They explained this effect as the result of a carotid sinus reflex. However, Luisada and Contro (1953) proved that *the carotid body* was involved (not the carotid sinus) and that lack of oxygen in the solution was more important than perfusion pressure. This interpretation was confirmed by the proof that carotid body stimulation causes a reflex dilatation of the pulmonary vessels which is mediated by vagal fibers (De Burgh Daly and De Burgh Daly, 1957). The same method was used by the author for evaluating the useful action of alcohol vapor administered by inhalation.

LESIONS OF THE CENTRAL NERVOUS SYSTEM

Von Frey first described the development of pulmonary edema following *vagotomy* (1867). Since then, a number of other authors have

observed the same phenomenon (Wolf; Schiff; Schafer, Weiser, Farber). Kraus, Brunn, and Farber found that pulmonary edema could be precipitated in vagotomized animals by intravenous infusion of fluids.

Farber studied the pathogenesis of pulmonary edema due to interference with the nerves to the lungs and found that the paralysis of the vocal cords is not a cause of the pulmonary edema, but that the real cause is the *loss of the innervation of the lungs.*

The fact that the sympathetic fibers are still intact was claimed, however, as the real cause by Jarisch, because removing the vagal impulses prevented the counteracting of the effects of the impulses of the sympathetic nerves (see below).

Other lesions of the central nervous system *may produce edema of the lungs.* Thus, Brown-Séquard found that stimulation of the stellate ganglia caused pulmonary edema. Joreš reported the occurrence of pulmonary edema after electrical stimulation of the hilus of the lung or the peripheral end of the cut vagus nerve, but Kotowschtschikow was unable to confirm his findings. However, when Teissier and Guinard combined stimulation of the peripheral end of the cut vagus nerve with *increased intrapulmonary pressure,* they claimed to have caused the development of pulmonary edema.

Jarisch et al. further showed that it is possible to provoke acute pulmonary edema in rabbits, rats, and guinea pigs by the suboccipital injection of veratrine. The edema may be prevented by injection of certain anesthetics (chloral hydrate and urethane), not by others; it may be prevented by large doses of atropine but not by cutting the vagus. The animals show an extreme arterial hypertension, severe tachycardia, and many signs of central excitation. The author and his coworkers (1957) used this method for the study of pulmonary edema in dogs. They showed through cardiac catheterization and transillumination of the lungs that, even though an increased venous return is the most important cause of pulmonary flooding, important pulmonary vascular reflexes also contribute to the increase of pressure in the pulmonary capillaries. A similar method, involving the injection of thrombin and fibrinogen into the cisterna magna was described by Cameron and De. This method was later used by Sarnoff and coworkers, who concluded that stimulation of the medullary centers produced increase of peripheral resistance (arterial and venous) and redistribution of the blood, followed by pulmonary hypertension.

IRRITATING SUBSTANCES IN THE LUNGS

Studies of pulmonary edema due to the inhalation of toxic or irritating substances have been made by many authors (Winternitz; Lambert; Mayer and Morel; Biondi, Melli). Changes in the permeability of capillaries caused by the action of toxic substances are well recognized and explain the pulmonary edema caused by war gases and other poisonings, and possibly that of pneumonia as well.

It has been known for many years that, after the inhalation of salt or fresh water, such as occurs in drowning, edema of the lungs develops, as manifested by the presence of large amounts of protein in the fluid in the lungs. Laqueur and De Vries Reilingh (1920) studied pulmonary edema due to inhalation of salt solutions and ascribed the resultant edema to the osmotic effect of the solution. Cameron and Neuberger (1937) showed that ketene has an action similar to phosgene and causes pulmonary edema in mice. They admitted a direct action on the protoplasm of the lung capillaries increasing permeability to plasma. Phosgene was also studied by Coman et al. (1947). Short (1942) had previously demonstrated that it causes a splitting of the mitochondria of the capillary endothelium, an early cellular response to injury. Cameron and Courtice (1946) showed that pulmonary edema is paralleled by a decrease in plasma volume and an increased concentration of the blood. As edema develops, pulmonary lymph flow steadily increases, as first shown by Drinker. Blood transfusion was proved extremely dangerous in experimental animals at this stage.

Ozone seems toxic for the capillary endothelium and causes pulmonary edema in mice (Mittler et al., 1956). Mittler (1958) further found that antifoaming agents do not help in this type of edema. Polli and Musiker (1958) produced pulmonary edema in rats by means of chlorine gas inhalation. They found that alcohol vapor or silicones administered by

aerosol were only moderately helpful, while parenteral morphine was seen to have a remarkably beneficial action. Rothlin successfully treated mild phosgene gas pulmonary edema with ergot alkaloids.

PULMONARY EMBOLISM

This type of experimental pulmonary edema has been studied by several authors including Katz et al. (1955) and Moreau et al. (1957). It is typical that localized embolism may cause diffuse pulmonary edema.

PULMONARY EDEMA DUE TO CHEST TRAUMA

Chest trauma, even if limited in extent, may cause diffuse, bilateral pulmonary edema. Daniel and Cate (1948) investigated the mechanism of this experimental form of edema and found that sympatholytic drugs prevented the diffusion and extension of the edema and saved the animals.

TOXIC PULMONARY EDEMA

Several poisons cause pulmonary edema in experimental animals. Among them, ingestion or intraperitoneal injection of ammonium salts causes pulmonary edema in cats, rabbits, rats, and guinea pigs, as shown by Windle et al. (1946), Koenig and Koenig (1948), McKay et al. (1949) and Cameron and Sheikh (1951). This type of pulmonary edema is usually preceded by severe hypertension and can be prevented or inhibited by adrenergic blocking agents. ANTU has a similar effect. *Alloxan* causes pulmonary hypertension and edema in the dog (Aviado and Schmidt, 1957). The most important cause of edema is a constriction of the pulmonary venules, as shown by the latter two authors and confirmed in the writer's laboratory.

13

Pathogenesis of paroxysmal pulmonary edema

ALDO A. LUISADA

The mechanism of production of pulmonary edema has been explained in different ways. Most writers have attempted to evolve *one* theory which might apply to all causes of pulmonary edema. It is the author's feeling that this is not feasible, and that different mechanisms should be advocated.

The oldest theory, advanced by Cohnheim and Welch (1878), postulated an *acute left ventricular failure causing a rise of* pulmonary venous pressure (backward failure), and then pulmonary edema. This theory met with wide acceptance, and is even now still invoked. Several objections can be raised: (1) Many patients with pulmonary edema exhibit a normal left ventricle, and the initial sequence of events involves either the central nervous system or the lungs, some patients have severe mitral stenosis or cor pulmonale, and the right ventricle is the only cardiac chamber under strain. (2) Patients with acute left ventricular failure may die in shock (cardiogenic shock) without pulmonary edema. This seems due to the fact that pulmonary capillary pressure rises only if there is good venous return to the right heart with a strongly active right ventricle.

A second theory was advocated by Teissier (1900). Disregarding cardiac elements, he considered pulmonary edema to result from an active, *sudden dilatation of the pulmonary vessels*. Even though this theory could not be accepted, reflex changes of the pulmonary vessels have been considered important by Cameron and Kuo, as well as by the author and his coworkers, who actually proved their existence. The following experimental data seem to confirm the importance of these reflexes in the production of pulmonary edema, even though they may also be interpreted according to a third theory (see below): (1) Bilateral stellectomy is effective in preventing pulmonary edema caused by intravenous epinephrine injection in the rabbit. (2) Rapid infusions produce different results, depending upon whether they are given intravenously or injected into the carotid arteries. Denervation of the carotid sinus area prevents this type of pulmonary edema. (3) Anesthetics, sedatives, and sympatholytic drugs are effective in preventing most types of pulmonary edema. Digitalis is poorly effective.

Another theory, already advocated by Peserico (1930), was revived by Sarnoff (1952), who called it "neurohemodynamic pulmonary edema." It emphasizes *the massive displacement of blood from the greater to the lesser circulation*, caused by strong sympathetic stimulation, acting on the peripheral vessels.

Theoretically, it is possible to distinguish between intracellular, *interstitial, and intraalveolar* types of edema of the lungs. Logically, the latter is the final stage, which is necessarily preceded by the others. Even though the first two stages are the most important in the mechanism of the edema, the third is the most vital for the patient because the alveolar fluid

TABLE 18-4. DIRECT DETERMINANTS OF PULMONARY CAPILLARY PRESSURES *
(from Visscher et al, 1956)

Variable	*Direction of change*	*Direct effect on pulmonary capillary pressure*	*Effect on pulmonary venous pressure*
Pulmonary arteriolar bore	Constriction	Fall	Fall
	Dilatation	Rise	Rise
Pulmonary venule bore	Constriction	Rise	Fall
	Dilatation	Fall	Rise
Pulmonary artery pressure (without arteriolar bore change)	Rise	Rise	Rise
	Fall	Fall	Fall
Pulmonary venous or left atrial pressure	Rise	Rise	(Pulmonary venous pressure is the determining variable)
	Fall	Fall	

* Considering in each case a change in only one variable at a time

prevents an adequate ventilation of the alveoli, thus impairing the gas exchanges in the blood. It is, moreover, important to consider the role of fluid having a high viscosity for the mechanics of alveolar respiration. According to Neergaard (1929), the surface tension of an extremely thin layer of fluid coating the alveolar endothelium is of great importance in the resistance of the lung to distention or compression A change in surface tension (plasma vs. water) might cause a complete transformation of pulmonary dynamics. Even more important would be the presence of fluid in the bronchioles Moreover, the viscous proteins of the bronchioles tend to "bubble," further increasing the volume of the exudate and its resistance to ventilation This point will be further discussed under "therapy" (antifoaming drugs).

Three elements are undoubtedly of paramount importance in the mechanism of pulmonary edema: (1) increase of pulmonary capillary pressure; (2) increase of pulmonary capillary permeability, (3) decrease of colloid osmotic pressure of the plasma. They will be examined separately and in detail.

INCREASE OF PULMONARY CAPILLARY PRESSURE

It is obvious that any study of this factor should include a complete consideration of all cardiac and vascular elements which may affect pulmonary capillary pressure. Because of the dynamic connections between greater and lesser circulations, both of them should be investigated.

An extensive literature is available on the dynamics of the pulmonary circulation in various types of animal preparations (Table 18-4). The applicability of these observations to clinical conditions is difficult to evaluate for several reasons: (1) the unphysiological nature of the animal preparations including the introduction of measuring devices into various parts of the pulmonary circulation,[1] and frequently accompanied by a good deal of shock; (2) the cutting of nerves which, though it may bring out mechanical relations, yields results which have no necessary similarity to the physiology of the intact animal, (3) use of anesthesia and artificial respiration, which are known to alter cardiac and respiratory dynamics; (4) differences between animal species; and (5) lack of unanimity concerning results reported by different investigators. Another source of difficulty is possibly the fact that a majority of the studies on the pulmonary circulation are based on changes in pressure in its various portions, whereas Hochrein and associates have shown that enormous changes in the volume of the capillary bed may occur as a result of altered dynamics.

[1] In this respect, modern techniques are definitely better than older ones. At present, catheterization of both halves of the heart can be done in animals with closed chest and limited trauma.

with little or no change in pressure This is probably connected with the negligible resistance to dilatation of the pulmonary capillaries due to the absence of significant tissue pressure, such as is found elsewhere in the body.

In the *heart-lung preparation*, according to Fuehner and Starling, increasing the strain on the left ventricle by increasing the peripheral resistance causes a rise in pressure in the pulmonary circuit. However, Anrep and Bulatao criticized these experiments on the basis that the inflow into the right ventricle was not maintained at a constant level[2] Welch and Kotowschtschikow noted a proportionate rise in pulmonary arterial pressure, when the aortic pressure increased following ligation of this vessel, by leaving open some of the large arteries of the aortic arch Katz and Wiggers found that ligating the aorta in a relatively intact animal caused no change in pulmonary arterial pressure On the other hand, in open chest experiments, every increase of inflow to the right heart, and every increase in the load on the left ventricle raises the pulmonary vascular pressures (Weber, and many others)

Lambert and Gremels found that a rise in pulmonary arterial pressure occurs in heart-lung preparations when pulmonary edema is developing, it is impossible to state whether the change in the pulmonary arterial pressure is related to the cause or effect of the pulmonary edema Cataldi found that the development of pulmonary edema in animals following the injection of irritating substances into the ventricular wall was also associated with a rise in pulmonary arterial pressure and a fall in systemic pressure, irrespective of whether it was the left or the right ventricle which was damaged. Farber described in detail the gross and microscopic changes in the lungs during the development of pulmonary edema in animals He observed the fact that frank pulmonary edema is always preceded by a period during which only intense congestion is present.

Of importance are the observations of a number of authors on pulmonary edema of diverse origin, in various types of preparations (Matsuoka, Newton, Barry, Kraus, Brunn, Farber), indicating that, whenever the tendency toward the formation of edema of the lungs is present, its development is favored by whatever causes slower circulation or increase in the volume of the blood in the lungs.

Left atrial and pulmonary arterial pressures were measured in the dog by Renais et al. after injection of hypertensive drugs followed by saline infusions. According to them, left atrial hypertension was constant. Pulmonary edema occurred when left atrial pressure was higher than 30 mm Hg. Welch's theory of pulmonary edema postulated "a disproportion between the working power of the left ventricle and that of the right ventricle of such character that, the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart" As Visscher pointed out, Welch did not postulate a prolonged imbalance in output, obviously inconceivable, but only admitted a temporary imbalance leading to overfilling of the pulmonary bed Several factors may cause an increase of pulmonary capillary pressure.

1. *A high pressure of the pulmonary capillaries always follows an increase in the mean pressure of the left atrium due to increase of diastolic pressure in the left ventricle.* Obviously, the latter may be due to (1) weakness of the left ventricle (myocardial infarct, rheumatic carditis, metabolic disturbance, i e, *absolute left ventricular*[3] *failure*), or (2) inadequacy of the left ventricle to empty itself completely in the presence of extremely high peripheral resistance or extremely high venous return (hypertensive crisis, extreme vasoconstriction with redistribution of the blood, thyrotoxicosis, beriberi, anemia, i e, *relative left ventricular failure*) Animal experimentation usually succeeds in provoking pulmonary edema through the second mechanism but, in clinical cases, the first may operate too, though possibly only as a concomitant factor The combination of the two (absolute plus relative weakness of the left ventricle) is probably common

The studies of Sarnoff have proved that a

[2] The tremendous increase of coronary flow gave an increased inflow to the right heart

[3] As a good output of the right ventricle is necessary for the production of pulmonary edema, it is obvious that a moderate left ventricular failure is more effective than a severe one Dramatic left ventricular failure usually causes cardiogenic shock and not pulmonary edema.

redistribution of the blood and an increase in venous return to the right heart, associated with an overload of the left ventricle, is the basis of the "neurohemodynamic pulmonary edema."

2. *A high pressure of the pulmonary capillaries always follows an increase of mean left atrial pressure without increase of left ventricular diastolic pressure.* This is typically found in cases of *mitral stenosis* (mitral block) or *insufficiency*. Clinically, mean pressures of 35 to 40 mm Hg can be observed without pulmonary edema. As these pressures are higher than the colloid osmotic pressure of the plasma,[4] it is likely that collateral pulmonary-bronchial anastomoses, well developed lymphatic drainage, and possibly structural changes of the capillary walls prevent the edema to a certain extent.

3. *High pressure of the pulmonary capillaries always follows constriction of the pulmonary veins.* This may be caused by the action of circulating substances (Mautner and Pick, Luisada; Aviado) or vascular reflexes, as proved in the author's laboratory (Aravanis et al).

It is obvious that *any increase in systemic venous return* or *intracardiac left-to-right shunt* will cause an important increase of pulmonary capillary pressure if there is left ventricular failure, mitral block, or pulmonary vein constriction On the other hand, pulmonary arterial constriction, while overloading the right ventricle, would *decrease* the pressure in the pulmonary capillaries and thus tend to prevent the edema (Table 18-4)

Whether or not *an acute dilatation of the pulmonary arterioles* may contribute to the edema in some cases, is an unsolved problem This possibility should be considered particularly in certain cases (mitral patients, congenital shunts), where pulmonary arterial constriction seems to prevent flooding of the capillaries Any relaxation of this vasoconstriction would favor pulmonary edema

Several researchers have investigated the possibility that nerve impulses, *directly acting on pulmonary vessels,* may influence the occurrence of pulmonary edema. Obviously, two possibilities were considered: (*a*) changes in caliber of arterioles, venules, or capillaries, or (*b*) changes in capillary permeability.

In one series of studies, Ferguson and Berkes (1957) submitted the lungs of animals to high arterial pressures (50 to 90 mm Hg in the arteries) while left atrial pressures were normal (4 to 5 mm Hg). *Edema occurred in denervated lungs at lesser pressures than those tolerated by innervated lungs.* This would lead to the belief that sympathetic tonus (of the arterioles?) is beneficial in preventing pulmonary edema.

Pulmonary edema caused by *vagal section is not affected by atropine and is prevented* by isopropylarterenol, as proved by Schmitt and Meyers (1957). This was interpreted as indicating that *a reflex loss of sympathetic tonus,* caused by vagal section, was involved (loss of afferent vagal impulses). Sympathetic inhibition prevents pulmonary edema caused by rapid intracarotid infusion, intravenous epinephrine, trauma to the chest, cisternal injection, ammonium-salt administration, or aortic ligation; this is undoubtedly due in large part to the effects on systemic vessels, but one might also postulate that changes of the sympathetic tonus of the pulmonary vessels are important in the mechanism of pulmonary edema. The last, still-missing link, is the demonstration whether this effect is purely mechanical or due to humoral agents

4. *Pulmonary capillary pressure* is increased by (*a*) redistribution of the blood with increase of pulmonary blood volume; or (*b*) increase of circulating blood volume. This fact, carefully investigated by Korner (1953) seems to be due to a *higher volume elasticity coefficient of the left atriovenous system in comparison with the right* (Opdyke et al , 1948).

CAPILLARY PERMEABILITY

Filtration Area. According to Visscher et al , there is an increase in filtration area whenever a larger number of alveolar capillaries are open. Increase of pulmonary capillary pressure, whatever the cause, would increase the filtration area.

Membrane Permeability. There seems to be a *linear relationship* between mean hydrostatic pressure in the capillaries and osmotic pressure of plasma proteins. With normal blood volumes, only the smaller particles escape from the blood; with increase in volume,

[4] This pressure was considered equivalent to 25 mm Hg by Starling; Fleury quotes the value of 32 mm Hg *in man.*

larger particles escape and appear in the lymph (Mayerson; Wassermann et al, 1955). This seems to prove that permeability of the wall is directly influenced by the degree of distention, a fact which had already been postulated by Krogh (1923).

Pulmonary edema fluid may vary considerably in protein content (Visscher et al) but this sheds no light on the mechanism for several technical reasons, including the possibility of addition of water in the air passages.

Membrane Damage. Observations in phosgene pulmonary edema (Hebb and Nimmo-Smith) seem to indicate that the disturbance occurs without changes of pulmonary capillary pressure[5] Then, two possibilities should be considered. direct damage to the endothelium or liberation of edematogenous substances

Hypoxia. The role of hypoxia in increasing pulmonary capillary permeability was stressed by C. Drinker However, several weaknesses of his theory were pointed out by Visscher et al including the fact that he ignored the role of changes in pulmonary venous pressure as a result of hypoxia

Capillary-wall Rupture. Microscopic or gross hemorrhages in the lungs are common in pulmonary edema. While "fragility" of the capillaries may be increased by poisons and inhalant gas, it is obvious that, in most cases, rupture of the capillary walls is caused by severe increase of internal pressure This has been confirmed by Kisch through use of the ultramicroscope.

Secretory Function of the Endothelium? The process of pulmonary edema has been investigated in experimental animals by Kisch (1958) by means of the electron microscope He demonstrated that, during an attack, both the ciliated and nonciliated cells secrete droplets of protein into the alveolar ducts (Fig. 18-14) This process requires further investigation because it may be of extreme importance in elucidating the mechanism of edema if some of the fluid is secreted by other cells than those of the capillaries.

Edematogenous Substances Acting on Permeability? The possibility that specific substances may act on capillary permeability was discussed by the author in 1930. At that time, *histamine* and *acetylcholine* were particularly considered. More recently, *serotonin* has been added. Serotonin seems to have several effects on the lungs. on the one hand, it constricts the arterioles and dilates the capillaries; on the other, by acting on a "permeability-globulin precursor," it seems to increase permeability of the endothelia (Spector, 1957). Both histamine and serotonin seem to have a similar mechanism and both are inhibited by several so-called "antihistaminic" drugs. If this mechanism is accepted, certain humoral connections, so far poorly understood, become clear. Splenectomy, useful in experimental pulmonary edema of the rabbit (Tremonti; Polli and Luisada) could act by preventing a sudden liberation of serotonin by the contracting spleen. Heparin, found useful in experimental pulmonary edema of the dog (Luisada and Contro) might act by inhibiting this mechanism (Spector). Further, the useful effect of adrenocortical steroids in preventing pulmonary edema (Schlechter et al., Polli and Luisada) could be, at least partly, connected with this same mechanism.

[5] Experiments in progress in the author's laboratory seem to confirm this in chlorine gas pulmonary edema.

DECREASED OSMOTIC PRESSURE OF THE BLOOD

This occurs after prolonged saline infusions, in lipoid nephrosis, starvation, or liver diseases As the effect of this factor is widespread, pulmonary edema due to decreased osmotic pressure is either part of a diffuse anasarca or is favored by other factors acting on the lungs.

GENERAL CONCLUSIONS

It should be kept in mind that most elements of pulmonary edema are interrelated· chemical and endocrine products may cause vasoconstriction and changes of permeability, blood pressure changes may cause reflex release of hormones or chemicals, and neurogenic elements may act through either the vasomotor system or hormones Moreover, the part played by the various factors differs according to the various causes and associated elements of pulmonary edema

Certain conclusions reached by experimental workers have a special importance.

Stimulation of the brain or the carotid body leads to direct or reflex *stimulation* of the sympathetic system, followed by severe vaso-



A



B

Fig. 18-14. A. Alveolar duct of a rabbit in acute pulmonary edema. ×13,000. One ciliated (C) and three nonciliated cells (NC) with their nuclei (N). The arrows indicate fine droplets, one of them still connected with the cell. In the ciliated cell, vacuoles near the surface, one of them (x) seems to just penetrate the surface. B. From the same animal, one ciliated and one nonciliated cell. Arrows indicate bunches of little droplets, still connected with the cell. On top, a big droplet in contact with some cilia. Pictures (A) and (B) prove that the epithelial cells are the source of part of the fluid produced in pulmonary edema. Under normal conditions, the secretion of these cells can be seen only rarely and very sparingly. (*Courtesy of B. Kisch.*)

constriction. This leads to increased peripheral resistance with increased loading of the left ventricle; displacement of a large mass of blood from the arterioles, capillaries, and blood reservoirs towards the veins, increased venous return; and, finally, filling of the blood vessels of the lungs with a large quantity of blood. In other words, this stimulation causes an increased output of the right ventricle, and, at the same time, increased difficulty in the emptying of the left ventricle This mechanism assumes great importance if there is left ventricular strain, and even more so if there is left ventricular failure Whether or not it is sufficient to cause pulmonary edema when the heart is intact is still open to question

MECHANISM OF CLINICAL FORMS OF PULMONARY EDEMA

The following considerations attempt to explain some clinical forms of pulmonary edema

Pulmonary Edema Following Massive Myocardial Infarction. When the power of the left ventricle is suddenly decreased, there occurs a marked increase of left atrial and pulmonary capillary pressures However, the latter persists only if an adequate venous return is maintained Therefore, a severe (but not too severe) lesion of the ventricle is the most effective. A peripheral mechanism initiated by cerebral ischemia, carotid-sinus hypotension, or carotid-body hypoxia, may contribute to the disturbance by causing peripheral vasoconstriction The accumulation of blood in the lungs is therefore probably due to both a cardiac and a vascular mechanism

Pulmonary Edema of Patients with Hypertension, Aortic Insufficiency, or Aortic Stenosis; of Cases with Minor Coronary Attacks; and Following Transfusion in Surgical, Obstetrical, Anemic, or Cardiac Cases. Left ventricular strain is followed by increase of left atrial and pulmonary venous pressures. Excitement, exposure to cold, fear of death, or exertion cause sympathetic stimulation and redistribution of the blood, with its accumulation in the lungs, thereby favoring acute pulmonary edema. The increased peripheral resistance may transform ventricular strain into ventricular failure. Or else, transfusions or infusions further favor the edema by increasing the quantity of blood in the lungs and lowering osmotic pressure.

Pulmonary Edema of Nephritic Patients, Especially If Uremic. A mechanism similar to the above can be postulated. Retention of metabolites increasing capillary permeability (nephritis), or decreased osmotic pressure of the blood (nephrosis), may be among the favoring causes.

Pulmonary Edema Following Trauma to the Skull or Lesion of the Central Nervous System. In this type, there is severe central sympathetic stimulation. This causes vasoconstriction and increased resistance placing a severe load on the left ventricle; it also leads to redistribution of the blood and its accumulation in the lungs. While these elements favor pulmonary edema, other factors should also be taken into consideration, such as dilatation of pulmonary arterioles or constriction of pulmonary venules and liberation of substances increasing capillary permeability (histamine, serotonin, hyaluronidase, etc).

Mitral Stenosis. The outflow of blood from the lungs is impeded by the mitral block, even during rest Sympathetic stimulation caused by excitement, exertion, exposure to cold, anger, or fright leads to (1) *tachycardia*, with shorter diastoles and impaired emptying of the left atrium, and (2) *vasoconstriction*, with redistribution of the blood and its accumulation in the lungs. The effect of the mitral block is proportionally increased by greater venous return to the heart

Exposure to Toxic Gases; Asphyxia. Here, the most important effect seems to be damage to the capillary endothelium followed by liberation of substances increasing capillary permeability. The role of reflexes arising in the mucosa of the respiratory passages is still to be evaluated These reflexes and the effect of hypoxia have special importance in cases of strangulation, asphyxia, or drowning

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Therapy of paroxysmal pulmonary edema

ALDO A. LUISADA AND LUIGI CARDI

Considering the multiple causes and the various mechanisms which may be involved in pulmonary edema, it is not surprising that a multiplicity of drugs and physical methods has been employed in its treatment. Unfortunately, tradition, on the one hand, and erroneous concepts, on the other, have thus far prevented a rational approach; while little agreement exists between different groups of physicians, each group treats all cases of pulmonary edema in a similar method.

DRUG THERAPY

Morphine. The value of morphine has been demonstrated in various types of experimental pulmonary edema. Morphine terminates most of the mild and some of the severe attacks, the best results being obtained in cases with hypertension, uremia, or mitral stenosis. The untoward effect of morphine in cerebral episodes and in chronic cor pulmonale should limit its use in such cases. The deleterious effect of morphine on the fetus may indicate the need for a cautious use of this drug in attacks occurring during pregnancy Even in cases of coronary occlusion, large doses of morphine may favor the onset of shock.

The mechanism of action in morphine administration is not completely known. It depresses the respiratory center and decreases the suction effect of dyspnea (which in turn may decrease edema) In therapeutic doses, morphine causes no apparent changes in cardiovascular dynamics. Pulmonary arterial pressures of cardiac patients, studied by catheterization, decreased in 26 out of 34 cases, but increased in the other 8 (Lenègre). It is, therefore, difficult to foresee whether the effect of morphine will be beneficial in a given case. Alleviation of anxiety and interruption of harmful reflexes is a useful action of morphine, especially in coronary patients. Vomiting caused by this drug may be deleterious. Morphine decreases the basal metabolic rate; this should decrease the work of the heart and lower venous pressure. However, it may take time for this effect to become apparent.

Morphine is administered subcutaneously in doses of 10 to 15 mg. It may be given intravenously

Atropine. Atropine (or belladonna) was used empirically in England for a long time before any publication described its effect in pulmonary edema.

Atropine was found either mildly beneficial or harmful in animals, when pulmonary edema was induced by means of epinephrine or rapid intracarotid infusion. Atropine does not improve pulmonary edema caused by ingestion of ammonium chloride, while it is beneficial in pulmonary edema caused by lesions of the central nervous system. The latter effect seems due to its prevention of extreme bradycardia, one of the possible factors of pulmonary congestion.

The clinical use of atropine should be limited to neurologic conditions with bradycardia and to some cases of coronary occlusion, also presenting bradycardia. In other cases, the tachycardia caused by atropine, as well as vagal inhibition in general, may be detrimental. Bronchodilatation caused by atropine has been considered either harmful or useful according to different theories.

For the above reasons, *Demerol*, a drug with both an atropinelike and a morphinelike action, should *not* be preferred to morphine, except in cases with a definite indication for the use of atropine. Moreover, Demerol has only moderate effects in decreasing anxiety.

Barbiturates; Chloral Hydrate. Barbiturates and chloral hydrate have been shown to be of value in experimental pulmonary edema. Their intravenous administration in man was attempted long ago by Luisada (1928–1930) and their value in several cases of pulmonary edema was shown. However, these drugs may be ineffective and, in certain cases, one cannot escape the impression that the deep sedation produced by them hastens the patient's demise. Venous return is decreased by chloral and barbiturates, and it is only logical to avoid use of these drugs in patients of the second group, those in danger of shock.

Aminophylline. This drug is a mild vasodilator, a bronchodilator, and a stimulant of the respiratory center. The first action is useful, though inadequate, the second is of doubtful utility (see atropine), and the third is definitely detrimental. For these reasons, aminophylline should not be used in the emergency treatment of the attack. The routine use of aminophylline, practiced in certain hospitals, cannot be recommended.

Papaverine. Intravenous injection of papaverine in association with other drugs has been advocated by Luisada (1930). Papaverine is a smooth-muscle relaxant and a vasodilator. The usual dose is 100 mg intravenously. Possible objections to its use are (1) if the patient belongs to group 1 (high output), papaverine is too mild a vasodilator to be effective, (2) if the patient belongs to group 2 (low output), even a moderate decrease of venous return can be dangerous.

Amyl Nitrite. This drug is administered empirically by inhalation in some hospitals. It is very probable that its powerful vasodilator effect may be useful in certain hypertensive patients, in spite of its extremely short span of action. However, since this drug may dilate the pulmonary vessels, the authors do not recommend it, even in patients belonging to group 1. As far as patients in group 2 are concerned, the use of amyl nitrite presents the same dangers as that of other vasodilators.

Intravenous Calcium Gluconate. This drug, tried by Luisada in animals (1928) and man (1930) has been further used in clinical cases by Gubner. It is supposed to have a direct effect on capillary permeability but its moderate vasodilator action is probably contributing to its usefulness.

Mercurial Diuretics. Mercurial diuretics have been used intravenously for pulmonary edema in many hospitals. Empiric use of these agents undoubtedly rested on the hope of rapid dehydration obtained through the promotion of diuresis. This action, however, would hardly be adequate and timely for improving circulation during the attack. Another property of the mercurials was subsequently described when cardiac catheterization revealed that they cause an important drop of pressure in the right atrium and ventricle within 20 to 30 min. This drop in pressure is still unexplained, and may be due to venous constriction decreasing venous return. This effect should be considered useful in patients of group 1 (high output), but unwanted and possibly dangerous in patients of group 2 (low output).

Sympatholytic Drugs. Drugs inhibiting or preventing stimulation of the sympathetic system have been considered helpful, following the demonstration that bilateral stellectomy was useful in preventing pulmonary edema, and also that spinal anesthesia produced similar beneficial effects. In animals, sympatholytic drugs have been shown to favorably affect the course of edema caused by most experimental procedures. Like all hypotensive drugs, sympatholytics (*Dibenamine, Piperoxan, Hydergine*) and ganglionic blocking agents (*Arfonad*, tetraethylammonium chloride) may induce shock in patients of group 2. The lasting action of some of these drugs and the difficulty of counteracting their effect, whenever this proves to be harmful, are other definite disadvantages.

Digitalis Glycosides (Ouabain). According to the theory of left ventricular failure, attacks of pulmonary edema are caused by an acute

weakening of the left ventricle. Therefore, intravenous administration of drugs stimulating the myocardium, like *strophanthin (or ouabain)*, was advocated in the emergency treatment of these attacks and good results were claimed. More recently, intravenous *digitoxin* or *lanatoside C* was substituted for strophanthin, and in many hospitals intravenous digitoxin has become part of routine therapy. Small doses of ouabain have been advocated in pulmonary edema associated with cardiogenic shock.

This therapeutic concept presupposes (1) that the left ventricle can be stimulated (this may not be possible when the ventricular wall is damaged by recent coronary occlusion or by prolonged and severe coronary insufficiency); and, (2) that the right ventricle is not unduly stimulated by the drug, so that no further rise of pulmonary flow or pulmonary arterial pressure will take place. Both premises may be questioned in some of the cases

Digitalis glycosides may lower venous pressure; however, this effect is mainly due to improved function of the myocardium, and does not take place otherwise On theoretical grounds, digitalis and ouabain are useful in any of the many cases having only a "relative" failure, namely one caused by "overload" and not by metabolic imbalance. However, during the attack, digitalis glycosides may be detrimental to patients with myocardial infarction Experiments on the preventive or therapeutic effect of digitalization in experimental pulmonary edema have failed, so far, to show any benefit (Testelli and Musiker, 1959).

A special case should be made of patients with mitral stenosis In these patients, the high pressure of the pulmonary capillaries is caused by high right ventricular output in the presence of mitral obstruction Rapid digitalization, if performed during an attack, can increase the severity of the edema, and may even precipitate pulmonary edema by increasing right ventricular output while the outflow from the lungs is impeded by the mitral block. A striking demonstration was given by Lenègre Injection of 1.2 mg of digitoxin in a patient with mitral stenosis during catheterization was rapidly followed by pulmonary hypertension and pulmonary edema Morphine and venesection then lowered pulmonary pressure and caused cessation of foaming.

Antihistaminics; Antiserotonins. The concept that liberation of histamine was the final event preceding edema of the lung was advanced by Luisada and his coworkers (1950). This concept seemed to be corroborated by subsequent studies but is still far from being conclusively demonstrated. *Phenergan* seemed to give good results in experimental and clinical pulmonary edema. However, its usefulness was not confirmed. Some "antihistaminics" are also "antiserotonins" while all of them are central nervous system depressants. Therefore, the explanation of this effect may be different from that initially postulated. *Reserpine* seems to have useful effects in certain types of experimental pulmonary edema, a fact which might be explained by its antiserotonin action.

Heparin was found beneficial in pulmonary edema of the dog (Luisada and Contro). As other anticoagulants do not share this action, this effect might be attributed to modification of the serotonin permeability mechanism (see above) or, in general, to modification of capillary permeability.

Corticotropin (ACTH). Corticotropin has been found beneficial in acute pulmonary edema of rabbits. Considering that its effect was obtained after 4 days of treatment, this drug might be considered *in the prevention* of the clinical attacks, but not in their therapy.

PHYSICAL, PHYSICOCHEMICAL, REFLEX, AND SURGICAL TREATMENT OF PULMONARY EDEMA

Several physical or physicochemical procedures have been used. Some are effective and should be considered in certain cases.

A Hot Bath (Sitzbath). This procedure has been used empirically and may be of help, since it causes peripheral vasodilatation It is particularly indicated in patients with hypertension or aortic insufficiency.

Venesection or Application of Tourniquets. The former is an old procedure, which is extremely effective in patients with arterial hypertension or aortic insufficiency and in certain instances of mitral stenosis with high venous pressure. As the main result is decreased venous return, venesection is contraindicated in patients of group 2 because it may induce shock The general procedure is withdrawal

of 500 to 600 ml of blood from an antecubital vein by means of a 15 gage needle or after cutting the vein with a scalpel. If the *tourniquet* procedure is used, bindings are applied to the four limbs with a moderate pressure, each is released and reapplied every 20 to 30 min in order to avoid venous thrombosis.

Oxygen. Oxygen was used at first only on patients with pronounced cyanosis As hypoxia may occur in pulmonary edema either as a primary or as a secondary factor, the use of oxygen is undoubtedly rational Moreover, clinical improvement follows its use in certain cases It is unfortunate that foam in the bronchioles prevents oxygen from reaching many of the alveoli. Oxygen is usually administered in the form of 100 per cent oxygen and humidified in order to prevent drying of the mucosae As oxygen in high concentrations is irritant, its administration should be interrupted from time to time in order to allow periods of normal air breathing.

Pressure Respiration. Pressure respiration has been advocated in the treatment of pulmonary edema. The theoretical basis of this method is that the increased pressure in the bronchoalveolar system counteracts the high pulmonary capillary pressure and decreases transudation Following animal experimentation, Barach et al suggested breathing against a positive pressure of 3 to 6 cm water This procedure produced useful results in several clinical cases and seemed particularly indicated in pulmonary edema due to gas poisoning

It has been shown that positive-pressure respiration, by increasing intrapleural pressure, decreases venous return This procedure, which may be useful in patients of group 1, presents some danger in patients of group 2, where impending shock might be precipitated [1]

Spinal Anesthesia. Spinal anesthesia with Novocain was tried by Sarnoff and Farr with encouraging results in clinical cases of protracted pulmonary edema which were refractory to other therapy. The intensive vasodilatation which follows spinal anesthesia decreases venous return to the right heart and lowers pulmonary arterial pressure. It is likely that the mechanism of action and the contraindications of this technique are similar to those of sympatholytic drugs. It should be kept in mind, moreover, that *Novocain* was also found useful when administered by intravenous injection in clinical cases (Gottsegen and Kohen). The dose employed was 10 ml of 1 per cent solution Its mechanism is probably related to central nervous system depression, similar to that of the "antihistaminics" and sympatholytics.

Stellate Block. Stellate block proved useful in experimental pulmonary edema, when tried by a coworker of the author. Clinical use of this method was made in 1952 by Pierach and Stotz They blocked the right stellate ganglion with procaine in eight clinical cases of pulmonary edema with hypertensive, coronary, or rheumatic heart disease. Excellent results were reported The authors state that only the right ganglion should be blocked while block of the left would increase pulmonary congestion. Explanation of the mechanism of action, however, is only tentative

Compression of the Carotid Sinus. This procedure was advocated by Wassermann. It acts by causing a reflex vasodilatation. It is extremely effective in patients with hypertension and in general in those of group 1. It is contraindicated if there is danger of shock.

ANTIFOAMING OR DEFOAMING THERAPY

Pulmonary edema, whatever the initial cause, starts a vicious circle of events which tends to prolong the attack This cycle is based on high pulmonary capillary pressure, transudation and accumulation of fluid in the alveoli, foaming, and local hypoxia, which in turn leads to more transudation, more foaming, and more hypoxia. While procedures tending to lower pulmonary capillary pressure are undoubtedly the most effective in patients of group 1, these procedures are either poorly effective or actually dangerous in patients of group 2.

Since 1950, a new approach, that of attempt-

[1] While positive pressure obtained by an expiration valve definitely decreases venous return, positive-pressure respiration with modern apparatus causing *intermittent pressure respiration during inspiration* seems to increase intraalveolar pressure for only a brief time With this method, Miller and Sproule obtained good results in pulmonary edema, even when associated with shock. However, even this method seems to cause "profound disturbances of intrathoracic circulation" (Feinsilver, 1958).

ing to break the cycle by acting on the foaming process itself was tried in the authors' laboratory. It was shown long ago (Laqueur and De Vries Reilingh) that large amounts of fluid may be present in the air passages with little danger to life, as soon as the surface tension of the fluid reaches a critical point, foaming starts. This leads to extremely severe effects, partly through the enormous increase in volume (foam) and partly through modification of the normal alveolar function which is based upon surface tension effects between humid alveolar surface and air (Neergaard).

Since impairment of the normal gas exchanges of the lungs is followed by hypoxia, which favors increased permeability of the capillaries, the foaming process in itself may be responsible for the continuation of the attack, and may be a cause of death. If a modification of the surface tension of the foam is brought about, the bubbles burst, then, the fluid which formerly composed the thin separating layers, will occupy a smaller volume than the foam

Antifoaming or defoaming agents (ether, octyl alcohol, capryl alcohol, and ethyl alcohol) were tested in the form of vapors or aerosols in four different types of experimental pulmonary edema. While the use of long-chain alcohols did not seem to improve the outcome, ether had a mildly beneficial action and ethyl alcohol (ethanol) produced excellent results. The inhalation of oxygen with a high concentration of *ethyl alcohol vapor* was followed by a decreased mortality, a lower lung-body index, and the easy expectoration of fluid. The systemic effect of alcohol was slight, because it is only a mild sedative and vasodilator, and because of its poor absorption This was shown by the observation that beneficial effects of alcohol by other routes were obtained only when administered in doses which induced deep anesthesia.

Experimental studies have also been made by Reich et al. with *silicone* in ether or in water; both were found beneficial Several antifoaming agents including silicone mixtures were compared in experimental animals (Luisada and Cardi). Three agents were definitely beneficial. 10 per cent silicone in water, Freon, and ethyl alcohol Since Freon may present some dangers if administered for long periods, only alcohol and silicone were considered for clinical use. While alcohol yields superior results in experimental pulmonary edema induced by epinephrine, it has a moderately irritant effect on the bronchial mucosa. This should favor the use of aerosol solutions of *silicone* in forms of pulmonary edema caused by lung irritants (chlorine, etc.). Experiments in this direction, however, proved that antifoaming therapy is only moderately beneficial in this type of pulmonary edema. The effectiveness of silicone aerosol tends to support the opinion that the utility of alcohol vapor is not due to systemic effect, but rather to its effect on surface tension of the foam.

Several studies with antifoaming agents in clinical cases of pulmonary edema have been reported. At first, the tolerance for alcohol and the best method of administration were studied in normal volunteers as well as in cardiac patients without pulmonary edema. Two methods which gave excellent results are: (1) use of a face mask and a 20 to 30 per cent alcohol solution. This technique is especially suited for comatose patients; and (2) use of a nasal catheter and a 95 per cent alcohol solution. This method is to be preferred in conscious patients (Luisada et al., 1952).

In both methods, the alcohol is placed in the usual humidifier bottle, connected to an oxygen tank. The oxygen flow is kept at 2 to 3 liters/min for the first few minutes. Then, when the patient's mucosae become adapted to the irritant gas (local anesthesia?), the flow rate is gradually stepped up until, after 10 to 12 min, it reaches 9 or 10 liters/min, and is maintained at this level.[2]

By means of this technique, alcohol vapor was administered to 14 patients during 17 severe or extremely severe attacks of pulmonary edema. In 14 of the patients, previous conventional therapy had failed; in the other three, alcohol was the only therapy used. When oxygen-alcohol vapor was administered, the results were dramatically favorable in ten of the patients and definitely helpful in the other four.

It was noted that patients with severe attacks

[2] It should be emphasized that prolonged alcohol vapor treatment should be administered only by alternating periods of inhalation (30 to 40 min) with periods of rest (10 to 15 min) during which the patient is breathing air or oxygen. This prevents excessive absorption of alcohol which might lead to unwanted systemic effects.

responded most dramatically and that those with attacks of shorter duration had a more rapid recovery following alcohol vapor inhalation. Usually, subjective relief preceded objective improvement, so that the patient felt completely recovered even though some chest rales were still audible

The beneficial effects of alcohol vapor were also noted by Goldmann and Primiano in one obstetrical patient, by Gootnick and coworkers in two patients (one of them in shock), and by Weyl in seven surgical patients A further report summarized the results of alcohol therapy in 50 attacks (Goldmann and Luisada, 1952).

Another method was tried by Sadove: 12 per cent alcohol aerosol by face mask. His results were equally good.

Protracted pulmonary edema often starts suddenly but has a protracted course and is less likely to be a crucial issue for the prognosis Ten such cases, all of them in poor or terminal state, were submitted to alcohol vapor therapy, in spite of the fact that none was considered likely to survive Seven patients improved but the improvement was slower and less marked than in the acute attacks It was good in three, moderate in two, and minimal in two

Following these reports, alcohol vapor treatment of pulmonary edema was instituted in various hospitals It is unfortunate that, although the results are usually described as good, no other detailed clinical reports were published

The good results of another antifoaming agent, *2-ethylhexanol*, was stressed by Reich and associates, following its use in 14 unselected cases One-half of the patients showed a good response Other antifoaming agents are being tested by various investigators including Sadove

MANAGEMENT

Treatment of the Attack. At present, the directions for management of the attack are still tentative Further studies on the mechanism of action of the various drugs and physical procedures used in the different clinical types of pulmonary edema are necessary

Antifoaming therapy is compatible with any other drug or physical treatment Therefore, it is the viewpoint of the authors that, whenever possible, *all cases of pulmonary edema should be immediately treated with an antifoaming agent.* In cases of pulmonary edema due to inhalation of toxic gases, silicone aerosol may prove to be the agent of choice. While the patient is undergoing inhalation treatment, a thorough examination of the causes leading to the attack should be made, and their effects on the patient noted (pulse, blood pressure, electrocardiogram). After this routine examination, which may take from 20 to 30 min, and if the attack has not subsided, other procedures should be instituted.

Patients whose pulmonary edema is associated with hypertension or aortic insufficiency, stenosis, or coarctation, should receive 15 mg of *morphine*, and may also receive an intravenous injection of a *mercurial diuretic. Sympatholytic drugs* may be given but other hypotensive agents (e g, nitroglycerin, papaverine), having a milder action, may be preferred.

Cases with myocardial infarct and blood pressure above 100 (or above 120, if there was hypertension prior to the attack) should also receive 15 mg of *morphine*, 0 5 mg of *atropine* may be administered if there is marked bradycardia *Mercurial diuretics* may be given, but in small quantity (1 ml intravenously). If the blood pressure drops below 100 mm Hg, the dose of morphine should be not more than 10 mg, and no mercurial may be given. The same rationale applies to cases of rheumatic heart disease with mitral stenosis

Patients with cerebrovascular accidents should *not receive morphine* They may be given *atropine, mercurials*, and possibly, *chloral hydrate* by rectum or intravenously.

Morphine should be given only in small doses (5 mg) to patients who have inhaled toxic gases, even though it is beneficial.

Compression of the carotid sinus may be attempted in hypertensive patients.

Spinal anesthesia or *right stellate block* should be used only in cases of cerebrovascular accidents or hypertensive heart disease with protracted edema, which is refractory to treatment, and then only if blood pressure is high.

Venesection occasionally may be a lifesaving procedure It should be employed only in patients with hypertension, cerebrovascular accidents, mitral stenosis, or aortic insufficiency, who have high venous pressure or visible ve-

ing to break the cycle by acting on the foaming process itself was tried in the authors' laboratory. It was shown long ago (Laqueur and De Vries Reilingh) that large amounts of fluid may be present in the air passages with little danger to life; as soon as the surface tension of the fluid reaches a critical point, foaming starts. This leads to extremely severe effects, partly through the enormous increase in volume (foam) and partly through modification of the normal alveolar function which is based upon surface tension effects between humid alveolar surface and air (Neergaard).

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Cardiac catheterization in heart failure

PHILIP SAMET AND WILLIAM H. BERNSTEIN

Delineation of the varied *hemodynamic* patterns in congestive heart failure has been a natural consequence of the development of suitable techniques for catheterization of the right and left hearts and for determination of blood flow. Most data have been obtained via *right heart catheterization* by the peripheral venous route. *Left heart catheterization* has been approached by a variety of techniques, including transbronchial left atrial catheterization, posterior percutaneous left atrial puncture, direct anterior left ventricular puncture, retrograde arterial left ventricular catheterization, suprasternal left atrial puncture, left heart catheterization from the right heart via intracardiac openings, and transseptal left atrial puncture (Morrow, Braunwald, and Ross, 1960). The latter technique affords the most physiologic method of approach to the left heart. The *direct Fick principle* and the *indicator-dilution Stewart-Hamilton technique* have been utilized for determining cardiac output. Parameters of pressure, flow, and central blood volume have been evaluated either at rest or during exercise by the above techniques.

The normal pulmonary artery pressure at rest is below 30/10–15 mm Hg, systolic, diastolic and mean, respectively. Right ventricular pressure is normally less than 30/5, normal right atrial mean pressure is less than 6 mm Hg. Normal pulmonary artery wedge *pressure* is less than 13 mm Hg.

The zero level for these right heart pressures is 5 cm dorsal to the angle of Louis. In the authors' laboratory, the corresponding zero level for left heart pressures has been taken as 10 cm dorsal to the angle of Louis. Mean left atrial *pressure is then normally* less than 10 mm Hg.

Left ventricular *end-diastolic pressure* is normally less than 10 mm Hg.

Moderate *exercise*, producing a *100* to 200 per cent increment in oxygen consumption, results in an increase in right heart *pressures of* only a few millimeters of mercury. There is similarly little increase of left atrial mean and left ventricular end-diastolic pressures during exercise. Cardiac *output in the normal subject* at rest is *3.1 ± 0.4* liters/min/m². During exercise, the increase in output is related to the increment in oxygen consumption. The normal *exercise output increment* is 600 to 1,000 ml/100 ml increase in oxygen consumption.

Data for central, or so-called "pulmonary," blood volume are limited. In 76 normal subjects the pulmonary blood volume totaled 850 ml/m² B.S.A. (Lammerant, 1957). This value represents the total volume between the point of injection in the pulmonary artery and the sampling point in the systemic artery. The *true pulmonary blood volume* is the volume between the site of injection in the pulmonary artery and the sampling point in the left atrium. These data have been approached by separate determination of the pulmonary artery–systemic artery volume, and the left atrial–systemic artery volume. True pulmonary blood volume is the difference between these

nous engorgement. Its use in other cases is more questionable, even in the presence of venous engorgement. As an example, in patients with myocardial infarct and systemic venous congestion, venesection may precipitate shock.

Pressure respiration has, in general, a favorable effect in pulmonary edema. However, patients with cerebrovascular accidents and depression of the respiratory center may respond poorly to this treatment.

PROPHYLAXIS

It should be kept in mind that *transfusions of blood* and *infusions of plasma or saline strongly favor pulmonary edema*. Failure to consider this fact is responsible for many episodes of edema in medical and surgical wards. Moderation and wisdom in the administration of intravenous fluids may prevent many attacks, not only in cases with coronary or rheumatic heart diseases or anemia, but also in patients whose myocardium is less efficient because of anesthesia, surgical intervention, or infection.

Prevention of pulmonary edema in *hypertensive patients* can be obtained in two ways. (1) by decreasing the load placed upon the left ventricle (salt-poor diet, hypotensive drugs, sympathectomy, sedation), or (2) by stimulating the myocardium (digitalis glycosides). Both methods are extensively used. This may account for the impression that occurrence of pulmonary edema in these patients is less frequent than formerly.

Prevention of pulmonary edema in patients with *coronary* or *cerebrovascular diseases* is difficult; prevention of the arteriosclerotic process would be the answer. Central sedation, especially at night, may prolong the life of these patients.

Prevention of pulmonary edema in *rheumatic heart disease* is based on avoidance of excessive physical work, salt restriction, and use of diuretics and digitalization. Mitral valvotomy is effective in preventing attacks of pulmonary edema in patients with mitral block. In *acute rheumatic fever*, adrenocortical extracts are the best treatment whenever the myocardium is severely damaged. The same treatment may be lifesaving in *rheumatic heart disease with silent rheumatic carditis*.

Most of the other forms of pulmonary edema are caused by unpredictable and often unavoidable events. The incidence of pulmonary edema in these cases will be reduced following improvement of working conditions (decreased exposure to toxic materials), improvement of medical techniques (slow removal of serosal fluids, moderation in the administration of intravenous fluids, rational anesthesia), and improved therapy of infections, including those involving the heart or the nervous system.

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Cardiac catheterization in heart failure

PHILIP SAMET AND WILLIAM H. BERNSTEIN

Delineation of the varied hemodynamic patterns in congestive heart failure has been a natural consequence of the development of suitable techniques for catheterization of the right and left hearts and for determination of blood flow. Most data have been obtained via *right heart catheterization* by the peripheral venous route. *Left heart catheterization* has been approached by a variety of techniques, including transbronchial left atrial catheterization, posterior percutaneous left atrial puncture, direct anterior left ventricular puncture, retrograde arterial left ventricular catheterization, suprasternal left atrial puncture, left heart catheterization from the right heart via intracardiac openings, and transseptal left atrial puncture (Morrow, Braunwald, and Ross, 1960). The latter technique affords the most physiologic method of approach to the left heart. The *direct Fick principle* and the *indicator-dilution Stewart-Hamilton technique* have been utilized for determining cardiac output. Parameters of pressure, flow, and central blood *volume* have been evaluated either at rest or during exercise by the above techniques.

The normal *pulmonary artery pressure* at rest is below 30/10–15 mm Hg, systolic, diastolic, and mean, respectively. Right ventricular pressure is normally less than 30/5, normal *right atrial* mean pressure is less than 6 mm Hg. Normal *pulmonary artery wedge pressure* is less than 13 mm Hg.

The zero level for these right heart pressures is 5 cm dorsal to the angle of Louis. In the authors' laboratory, the corresponding zero level for left heart pressures has been taken as 10 cm dorsal to the angle of Louis. Mean left atrial pressure is then normally less than 10 mm Hg.

Left ventricular *end-diastolic pressure* is normally less than 10 mm Hg.

Moderate *exercise*, producing a 100 to 200 per cent increment in oxygen consumption, results in an increase in right heart pressures of only a few millimeters of mercury. There is similarly little increase of left atrial mean and left ventricular end-diastolic pressures during exercise. Cardiac output in the normal subject at rest is 3.1 ± 0.4 liters/min/m². During exercise, the increase in output is related to the increment in oxygen consumption. The normal exercise output increment is 600 to 1,000 ml/100 ml increase in oxygen consumption.

Data for central, or so-called "pulmonary," blood *volume* are limited. In 78 normal subjects the pulmonary blood volume totaled 650 ml/m² B.S.A. (Lammerant, 1957). This value represents the total volume between the point of injection in the pulmonary artery and the sampling point in the systemic artery. The *true pulmonary blood volume* is the volume between the site of injection in the pulmonary artery and the sampling point in the left atrium. These data have been approached by separate determination of the pulmonary artery–systemic artery volume, and the left *atrial–systemic artery* volume. True pulmonary blood volume is the difference between these

two volumes (Dock et al., 1961; Milnor et al., 1960). Data for the true pulmonary blood volume in the normal subject determined by the pulmonary artery and left atrial injection techniques are as yet unavailable.

The development of *clinical congestive heart failure* is accompanied by alterations in intravascular and intracardiac pressure levels, in intracardiac pulse pressure contours, in cardiac output, and in total blood volume (or some segment thereof). *Left ventricular failure* is characterized by elevation of the left ventricular end-diastolic pressure; elevation of left atrial mean pressure necessarily follows. Pulmonary venous and arterial pressure will eventually increase. Cardiac output may be normal, increased, or decreased, depending on the cause of the heart failure. Arteriovenous difference is increased in *low-output failure* but may be normal or decreased in *high-output failure*. Right ventricular end-diastolic pressure may be normal at this stage, i.e., there may be a pure left-sided failure (Cournand, 1952). Subsequent elevation of right ventricular end-diastolic and right atrial mean pressure signifies the development of *combined heart failure*. On the other hand, in chronic pulmonary disease, right ventricular end-diastolic pressure may be elevated in the face of normal pulmonary artery wedge pressure, and therefore presumably normal left atrial mean and left ventricular end-diastolic pressures, i.e., there may be a pure right-sided failure.

These concepts emphasize the purely hemodynamic approach to heart failure without entering into a discussion of the clinical counterparts of heart failure. Indeed, hemodynamic evidence of heart failure may exist in the absence of clinical manifestations thereof (McCord et al, 1953, Musser et al., 1956). Most observers feel that such hemodynamic evidence, i.e., elevation of ventricular end-diastolic pressure, is sufficient to define the existence of heart failure. According to an opposing view, elevation of ventricular end-diastolic pressure may be due to marked thickening of the ventricular wall per se, with alteration of the distensibility characteristics of the ventricle. Elevation of ventricular end-diastolic pressure, from this viewpoint, would *not* be equated with the existence of congestive heart failure.

The introduction of exercise studies into cardiac catheterization procedures (Hickam and Cargill, 1948) has demonstrated that heart failure may be absent in the resting state but may readily develop during even moderate exercise—as defined by an elevation in ventricular end-diastolic pressure without an appropriate increase in cardiac output (Richards, 1949).

In summary, therefore, *the basic hemodynamic characteristics of congestive heart failure consist of an elevation of ventricular end-diastolic pressure.* Cardiac output may be low, normal or increased. Depression of the cardiac output without elevation of ventricular end-diastolic pressure does not constitute hemodynamic evidence of heart failure. The hemodynamic evidence of failure may become more evident during exercise studies or may appear only then. Ventricular end-diastolic pressure may further rise; cardiac output may rise only slightly, remain stationary, or even fall during exercise (Hickam and Cargill, 1948, Lewis et al., 1953).

Characteristic *changes in pulse pressure contours* may develop in the congested state. The atrial pressure curve may take on the characteristics seen in atrioventricular valvular insuffi-

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of right atrial mean pressure and the development of *functional tricuspid insufficiency*. Typical, but not pathognomonic, alterations have been observed in the right atrial and right ventricular pressure curves of patients with *constrictive pericarditis*. The former curve has a distinct "W" form. The ventricular curve is character

pressure, [illegible]

a resultant small pulse pressure, and an *early diastolic dip*, down to a near-zero level (Bloomfield et al., 1946; Hansen et al, 1951; Harvey et al, 1953) (Fig 18-15). Similar pulse pressure contours have, however, also been observed in heart failure from other causes (Clark et al., 1956; Hetzl et al, 1953).

Emphasis has been placed on the mechanical aspects of cardiac function in heart failure. On the other hand, the role of the nervous system in the maintenance of systemic venous and pulmonary arterial hypertension in heart failure has been emphasized by Halmagyi (1952 and 1959).

Administration of dihydroergotamine to patients with chronic congestive heart failure (28 studies) 108

resulted in an increase in peripheral and central venous pressure in the absence of changes of systemic arterial pressure and cardiac output. A direct vasoconstrictor effect of dihydroergotamine on vascular smooth muscle was postulated as the cause of the rise in venous pressure. A number of drugs, including dihydroergotamine, Priscoline, Dibenamine, hexamethonium, morphine, reserpine, and acetylcholine, have been investigated for their potential vasomotor effect on the pulmonary circulation. Recent interest has centered on acetylcholine. Despite early promise, extensive intracardiac infusion of acetylcholine into the right heart in patients with mitral stenosis has failed to reveal a clinically significant consistent vasodilator effect at various levels of pulmonary hypertension (Samet et al, 1961, 1962).

Cardiac metabolism in the nonfailure and congestive heart failure states has received considerable attention (Olson, 1959, Danforth et al, 1960). The high-output failure seen in anemia and beriberi has been related to a defect in myocardial energy production caused by a reduced capacity for hydrogen transport. The more commonly encountered low-output failure of hypertensive and valvular heart disease is apparently related to a defect of the myosin component of actomyosin. It is quite likely that future advances in this field will result in *fruitful therapeutic advances.*

The hemodynamic patterns noted during cardiac catheterization in the commonly observed causes of heart failure will now be outlined

RHEUMATIC HEART DISEASE

The development of surgical therapy for rheumatic valvular heart disease has resulted in extensive studies of the hemodynamic status of subjects with this disease, both with and

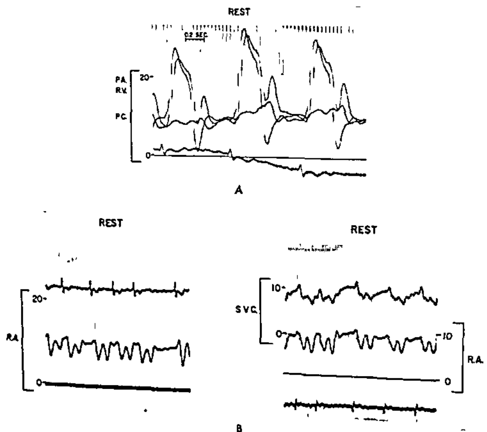


Fig 18-15. A. Pulmonary artery, right ventricular, and pulmonary artery wedge pressures in constrictive pericarditis. The diastolic dip on the right ventricular curve is to be noted. B Right atrial and superior vena cava curves in constrictive pericarditis The "W"-shaped curves are readily noted

without heart failure. The concept of *pure* left or right ventricular failure has been validated—elevation of left ventricular end-diastolic pressure with normal right ventricular end-diastolic pressure, as in aortic stenosis, or elevated right ventricular end-diastolic pressure in the face of normal left ventricular end-diastolic pressure, as in mitral stenosis.

Hemodynamic studies *during acute pulmonary edema* have revealed consistent changes.

Finlayson et al. (1961) studied 5 patients, 2 with pure mitral stenosis, 1 with mitral stenosis and systemic hypertension, 1 with mitral and aortic stenosis, and 1 with aortic regurgitation. The mean pulmonary artery pressures were 57, 76, and 37 mm Hg before, during, and after recovery from pulmonary edema. In 2 patients, mean pulmonary artery wedge pressure was 25 before pulmonary edema, this pressure rose to 39 mm Hg during pulmonary edema. Cardiac index changed little during pulmonary edema, but the heart rate rose from 101 to 122. In 2 patients, right ventricular end-diastolic pressure fell from 26 to 5 and from 15 to 4 mm Hg after recovery. Intravenous *hexamethonium* (6.5 to 25 mg) was given by cardiac catheter in 4 subjects and produced a rapid and dramatic clinical response. Fejfar et al (1959) studied 5 rheumatic patients under similar circumstances—4 with mitral stenosis and 1 with mitral insufficiency. The development of *dyspnea* was associated with a rise in pulmonary artery and pulmonary artery wedge pressure. Cardiac output fell only moderately. There did not appear to be a relationship between the degree of dyspnea and the decrease in output. Arterial oxygen saturation fell during pulmonary edema to as low as 60 per cent in 1 subject. Lenègre and Scébat (1952), as well as Hayward (1955), also recorded sharp increases in pulmonary artery and pulmonary artery wedge pressures during pulmonary edema. Little

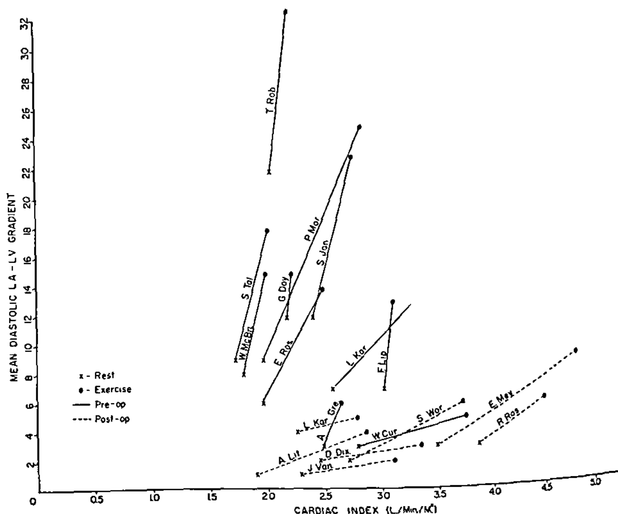


Fig. 18-16. Relationship between mitral diastolic gradient and the cardiac index in patients with mitral valve disease. The clear separation in the rate of change of gradient between the pre- and postoperative patients is apparent. W. Cur. is a possible example of the myocardial factor in mitral stenosis. A. Gre. is an asymptomatic woman with auscultatory evidence of mitral stenosis.

change in cardiac index was observed. These observations were made in subjects with pure mitral stenosis. Reductions of arterial oxygen saturation to levels as low as 45 per cent were observed. Gorlin et al. (1951) *made similar observations* in 8 patients with mitral stenosis studied at rest and in 3 such patients who developed pulmonary edema during exercise. All had pulmonary artery ... mm Hg. Cardiac index

... during pulmonary edema are not available at present, but limited observations at rest and during exercise are available in subjects with mitral stenosis not in pulmonary edema at *the time of study.* These data (Samet et al., 1959) show the expected sharp rise in left atrial mean pressure during exercise.

Comparison of patients before and after *mitral commissurotomy* revealed a marked difference in the rate of rise of left atrial pressure per unit increase of cardiac output during exercise (Fig. 18-16) The increase in left atrial pressure during *exercise is attributed to an increase* in both output and heart rate. The effect of the latter two parameters can be separated (Fig. 18-17) (*Silverman et al*, 1961). Comparison of left atrial and pulmonary artery wedge pressure revealed unexplained instances in which wide differences were observed *between these values* (*Bernstein et al*, 1960). Interesting artefacts in the recording of pulmonary artery wedge pressure were noted (*Fig* 18-18). These findings illustrate the potential hazards of drawing conclusions as to the level of left atrial pressure from the pulmonary artery wedge curve

Hemodynamic data are also available *in pure left heart failure of* rheumatic origin without clinically overt pulmonary *edema*

In 1 *subject* with mitral stenosis and insufficiency and aortic insufficiency (Harvey et al., 1949), studied *with* right heart catheterization, *control* cardiac index was moderately reduced (2 13 liters/min/m²), *and moderate pulmonary hypertension* was observed (58/31, 39) in the face of a normal right ventricular end-diastolic pressure, 3 mm Hg After digitalization, cardiac output and stroke volume rose 47 and 83 per cent, respectively Pulmonary artery pressure fell to normal levels Peripheral arterial resistance fell, and the heart rate decreased from 94 to 75 Yu et al. (1957) reported similar studies in 4 subjects with rheumatic heart disease—1 with aortic stenosis, 1 with predominant mitral insufficiency, and 2 with mitral

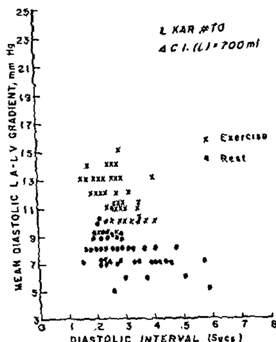


Fig. 18-17. Relationship between mitral diastolic gradient and the diastolic filling period at rest and during exercise. The increased exercise cardiac output results in larger exercise gradients at the same diastolic intervals as at rest.

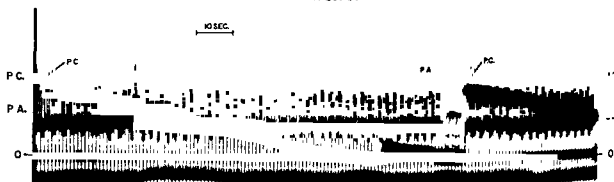
stenosis and insufficiency. Right ventricular end-*diastolic* pressure was normal. Control data revealed moderate to severe *elevation* of pulmonary artery mean and pulmonary artery *wedge mean* pressures. *Cardiac index* was markedly reduced in 2, slightly reduced in 1, and normal *in 1. Following digitalization* with *acetyl-strophanthidin*, the most consistent changes were *decreases* of pulmonary *artery* and pulmonary artery wedge pressures. Cardiac index rose *only minimally* in 3 subjects; an 18 per cent increase in output was *recorded in* the fourth *subject*

Failure of pulmonary artery pressures to return *to normal* levels following digitalization suggests the addition of mitral valve block, pulmonary vascular disease, *or* both to left heart *failure* as etiologic factors in pulmonary hypertension in these 4 subjects (Samet et al., 1958). The observed *fall* in pulmonary artery pressure *is*, however, highly suggestive of the coexistence of left heart failure. Harmanci et al. (1951) observed the acute effect of 1.5 *mg Cedilanid* given intravenously *in* 2 subjects with rheumatic heart disease, 1 with aortic stenosis, and 1 with *predominant* mitral *insufficiency*. *Control* right ventricular end-diastolic

pressure was normal. Moderate pulmonary hypertension was observed. *After digitalization,* pulmonary artery pressure again fell toward normal, but did not reach normal, and cardiac output rose. Similar studies of the effect of *acute digitalization in subjects with left heart* failure studied during combined right and left heart catheterization are not available as yet. However, Samet et al. (1959 and 1961) have made observations relative to heart failure during combined right and left heart catheterizations in patients with mitral and or aortic valve disease.

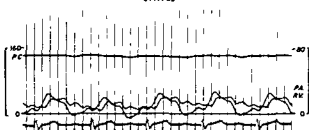
Pure right heart failure without left heart failure, i.e., a normal left ventricular end-diastolic pressure but elevated right ventricular end-diastolic pressure, has been observed in pure mitral stenosis. The converse, i.e., elevation of the left ventricular end-diastolic and *left atrial mean pressures without elevation of* the right ventricular end-diastolic pressure has been noted in patients with aortic stenosis, either at rest or during exercise. Elevation of left ventricular end-diastolic pressure to grossly abnormal levels (more than 20 mm Hg) has followed moderate exercise (doubling basal oxygen consumption) in subjects with rheumatic aortic stenosis. In one instance, left ventricular end-diastolic pressure rose to over 40 mm Hg (Fig. 18-19) without the development of clinical pulmonary edema or even dyspnea. Hancock and Fleming (1960) have also noted marked elevation of the left ventricular end-diastolic pressures in aortic stenosis; end-diastolic pressures as high as 48 mm Hg were observed in subjects studied at rest.

PULMONARY ARTERY WEDGE PRESSURES
AS AND AI CATH. # 155 (F. EUL)
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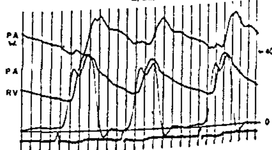
A

PULMONARY ARTERY WEDGE PRESSURES
ANOMALOUS PULMONARY VENOUS DRAINAGE



B

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C

Fig. 18-18. A. Pulmonary artery wedge (p c) and pulmonary artery pressures. The progressive fall in wedge pressure is an unexplained artefact. B. Right ventricular, pulmonary artery, and wedge pressures with a triple-lumen catheter The wedge pressure (uppermost curve) has the contour of a delayed pulmonary artery curve. C. Marked artefacts in pulmonary artery wedge pressure (P A.W.) result in obviously false elevation of wedge pressures far above the pulmonary artery pressure.

Elevation of pulmonary artery pressure after digitalization in patients with rheumatic heart disease and mitral stenosis has been reported on occasion Greene et al. (1961) have discussed the interplay of the various factors that may result in such an elevation of pulmonary pressure. *Restriction of the pulmonary vascular bed and increase in cardiac output after digitalization are probably the underlying mechanisms in such instances.*

Any discussion of the effect of *digitalis* in patients with mitral valve disease raises the question of the myocardial factor. Harvey et al. (1955b) first described a group of patients with mitral stenosis in whom the clinical difficulties and physiologic abnormalities were postulated to stem from *myocardial insufficiency* These patients exhibited little or no pulmonary hypertension at rest, cardiac output was normal or depressed at rest but did not rise normally during exercise The latter characteristic separated these patients from those with the murmur of mitral stenosis but without *clinically significant* mitral valve block or myocardial insufficiency. Surgical intervention in the myocardial insufficiency group (Ferrer et al., 1955) was felt to be of little value Fleming and Wood (1959) stated that similar cases were observed in 3 2 per cent of 750 patients with rheumatic mitral valve disease Right heart catheterization revealed a low cardiac output at rest. Left atrial pressure was measured *only indirectly*—from pulmonary artery wedge pressure levels This indirectly determined mean left atrial pressure was only 7 mm Hg Fleming felt that mitral surgery did not improve the clinical status of these subjects. Soloff et al. (1957) have also described a similar group of subjects Underlying the concept of the myocardial factor in mitral stenosis is the thesis that the mean diastolic left atrial–left ventricular gradient would be minimal in these patients, both at rest and during exercise The demonstration of this minimal mitral diastolic gradient, or of its absence, has rarely been made during left heart catheterization (Samet et al., 1959) *Indeed surgically significant mitral stenosis has been observed in some sub-*

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mitral stenosis, therefore, remains to be evaluated However, in one patient diagnosed after

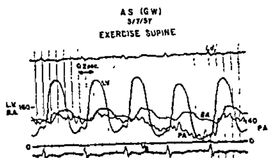


Fig. 18-19. Left ventricular, brachial artery, and pulmonary artery pressures during exercise in a patient with severe aortic stenosis. Left ventricular end-diastolic pressure is markedly elevated to over 40 mm Hg.

combined right and left heart catheterization, both right and left ventricular end-diastolic pressures were normal at rest but rose to abnormal levels during exercise despite a minimal mitral diastolic gradient at rest (4 mm Hg) and during exercise (7 mm Hg) (Samet et al., 1959).

Alternation of the pulse in either the lesser or greater circulation has been reported in catheterization studies in man Ferrer et al. (1956) recorded *alternation in the lesser circulation* in two patients with mitral valve disease; a third patient exhibited only systemic alternation. Cooper et al. (1958) noted *left ventricular alternation* in 15 of 28 patients with rheumatic aortic stenosis. *Alternation in the systemic arterial pulse* accompanied left ventricular alternation in all cases; the magnitude of the alternation was, however, greatly reduced in the systemic arterial pulse. In Cooper's study, *electrical alternans* was absent. Bernstein et al (1961) and Hancock and Fleming (1960) have also observed left ventricular alternation in aortic stenosis (Fig. 18-20).

In addition to the afore-mentioned right heart hemodynamic studies in acute heart failure and combined heart catheterization studies in mitral and aortic valve disease, a number of *enlightening studies* are available in patients with mitral stenosis employing right heart catheterization alone. Ferrer et al. (1952 and 1955) and Harvey (1955) have documented *the various causes of pulmonary hypertension in patients with mitral stenosis*, viz., mitral valve block, left heart failure, and pulmonary vascular disease. A decrease in pulmonary

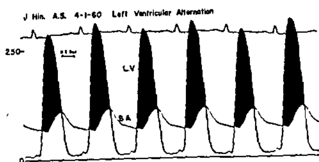


Fig. 18-20. Left ventricular pulsus alternans in severe aortic stenosis.

hypertension after digitalization pointed to *left heart failure* as at least a contributing factor to pulmonary hypertension. Gradual disappearance of pulmonary hypertension on repetitive right heart catheterization after mitral commissurotomy suggested *pulmonary vascular disease* as at least a contributing cause to elevation of pulmonary artery pressure. On the contrary, return of pulmonary artery pressure to normal levels immediately after mitral commissurotomy pointed to *mitral valve block* as the cause of pulmonary hypertension. The clinical picture of right heart failure was physiologically characterized by an elevation of the right ventricular end-diastolic pressure. Such elevation often developed during exercise, even when absent at rest. Cardiac index was usually diminished at rest and failed to increase normally during exercise.

The data of Samet et al. (1959) and Dickens et al. (1957) have clearly demonstrated that varying degrees of pulmonary hypertension may be associated with the same level of the mean diastolic left atrial–left ventricular gradient. Significant mitral valve block was found in the presence of normal, as well as elevated, pulmonary artery pressure. The presence of pulmonary hypertension cannot, therefore, be utilized as a measure of mitral valve block or as an indication for surgery

It should be emphasized that the significance of a mitral diastolic gradient must be interpreted with knowledge of the diastolic flow across the valve. A 5 mm Hg gradient flow with a cardiac index of 3 5 liters/min/m² connotes a valve size considerably different from one associated with the same gradient but with a cardiac index of 1.5 The hemodynamic evaluation of the effects of mitral commissurotomy is therefore difficult if right heart catheterization alone is employed, as by Donald et al. (1957)

Left heart catheterization is also of considerable value in the diagnosis of mitral stenosis in a select group of patients with very severe pulmonary hypertension; in these subjects, the murmur of mitral stenosis may be atypical in character or may even be absent. As described by Mackinnon et al. (1956), the physical signs are characteristic of severe pulmonary hypertension per se.

Cardiac catheterization techniques have been utilized to study coronary blood flow and myocardial oxygen consumption (Rowe et al, 1960). The results demonstrate a decrease in left ventricular coronary blood flow and a decrease in left ventricular oxygen consumption per unit weight of left ventricle.

Pulmonary blood volume, both total and true, as defined above, has been studied with cardiac catheterization techniques. Borden et al. (1949) first reported pulmonary artery to systemic artery volumes of 642 ml/m² in patients with rheumatic heart disease without signs of congestive heart failure. Lagerlof et al. (1949), Kopelman et al. (1951), Doyle et al. (1953), Rapaport et al. (1956), and Milnor et al. (1960) reported corresponding values ranging between 817 to 887 ml/m². These values are only slightly larger than those observed in normal subjects. True pulmonary blood volume, i.e., the volume between the pulmonary artery and the left atrium, has been determined by Milnor et al. (1960) and by Dock et al. (1961). These studies revealed true pulmonary blood volumes between 322 to 365 ml/m².

Physiologic studies by right and combined heart catheterizations in patients with rheumatic aortic stenosis have revealed that left ventricular failure with elevation of the end-diastolic pressure is not infrequently seen, as noted above. It is of considerable interest that the cardiac index has been found to be within normal limits, or even somewhat elevated, by both direct Fick and indicator-dilution techniques in patients with severe aortic stenosis with overt left ventricular failure (Hancock and Fleming, 1960; Dexter et al., 1958). Left heart catheterization has also revealed that many of the clinical features of aortic stenosis may be noted in symptomatic patients who are being considered for aortic commissurotomy—but significant aortic stenosis may not be present, as determined by the absence of a systolic left ventricular–systemic arterial gradient of any magnitude (Hancock et al, 1958).

Unnecessary cardiac surgery may thus be obviated.

ARTERIOSCLEROTIC HEART DISEASE

Hemodynamic data in *acute myocardial infarction* have become available in the past 10 years.

Freis et al. (1952) studied 11 patients with acute infarction. Cardiac output was measured by the *indicator-dilution technique*; T 1824 was injected via a polyethylene tube passed into an axillary or subclavian vein and was sampled from the femoral artery. Conditions of the patients were classified as (1) mild, (2) moderate and severe, and (3) with *cardiogenic shock*. The second group exhibited signs of congestive failure. The patients in the third group were severely ill, all eventually died. In the first group, cardiac index was normal—mean, 3.4 liters/min/m², heart rate, 92; stroke volume, 76 ml beat, and central venous pressure, 90 mm water. In the second group, cardiac index was 2.9 liters/min/m², heart rate, 101, stroke volume, 50, and central venous pressure, 120. In the third group, cardiac index was 1.8 liters/min/m², heart rate, 128, stroke volume, 27, and central venous pressure, 115. Central blood volume was similar in all three groups.

Gilbert et al. (1954) studied 20 patients with acute myocardial infarction by similar techniques. The first group (7 patients) exhibited neither heart failure nor shock, cardiac index was 2.61 liters/min/m², venous pressure was 130 mm water. The second group (6 subjects) was in cardiac failure, with an index of 1.9 liters/min/m² and a venous pressure of 167 mm water. All 7 subjects in the third group were in shock, with a cardiac index of 1.0 liters/min/m² and a venous pressure equal to 215 mm water.

Smith et al. (1954) made measurements of cardiac output in 9 patients with acute infarction without shock and in 6 with *shock*. Cardiac output was again measured by intravenous indicator injection with peripheral arterial sampling. In the patients without peripheral shock, cardiac index totaled 2.4 liters/min/m². After recovery, cardiac index increased significantly, to 2.7. In the 6 patients in shock, cardiac index was 1.65.

Gammill et al. (1955) investigated 37 patients with acute infarction. Cardiac output was determined by the indicator-dilution technique. Cardiac index was 4.25 liters/min/m² in the least severe group, 3.21 in the intermediate group, and 2.93 in the most severe group. On restudy 4 weeks after recovery, cardiac output in the third group had risen to the values in the first two groups. In those patients in shock, failure of peripheral vasomotor mechanism was not demonstrated.

Lee (1957) analyzed the data in 11 patients with acute infarction, utilizing similar techniques for determination of cardiac output. Cardiac index was normal, 3.7 liters/min/m², even in those patients in shock. The most consistent hemodynamic observation in these patients was an *elevated venous pressure*.

Broch et al. (1959) studied 35 subjects with acute myocardial infarction. Those in group I (18 subjects) were uncomplicated, those in group II exhibited shock or failure. *Indicator-dilution techniques* with peripheral venous injection were employed. The cardiac index in the first group was normal, 3.03 liters/min/m², this index was reduced to 2.04 in the second group. Stroke volume changes followed output data. Eight patients in group II died, 9 survived. The cardiac index in those that survived was 2.36; in the nonsurvivors the index was 1.73. On restudy 3 weeks after infarction, the patients in group I exhibited little change, while those in group II showed considerable improvement.

Cardiac dynamics in asymptomatic male patients with *healed myocardial infarction* were studied by Chapman and Fraser (1954). The infarcts had occurred at least 6 months before study. The cardiac index at rest was 2.95 liters/min/m². The increase in cardiac output during exercise was equivalent to that noted in a comparable group of normal subjects, indicating that a normal response to the stress of exercise could be expected in this type of subject.

Lewis et al. (1953) catheterized three patients with arteriosclerotic heart disease and heart failure. Cardiac index at rest averaged 1.73 liters/min/m². Stroke volume per square meter averaged 21 ml. Pulmonary artery wedge pressure (employed as an indicator of mean left atrial pressure) was 32 mm Hg. Pulmonary artery mean pressure was 44 mm Hg. During moderate exercise (oxygen consumption rose from 133 to 198 ml/min/m²), cardiac index rose to 1.9 liters/min/m², stroke index fell to 19 ml. Pulmonary artery wedge pressure rose to 39 mm Hg; pulmonary artery mean pressure increased to 57 mm Hg. Right atrial mean pressure data, obtained only at rest, averaged 18 mm Hg, indicating that right as well as left heart failure was present.

Bloomfield et al. (1948) studied the effect of intravenous *ouabain* in three patients with arteriosclerotic heart disease in *failure*. Control measurements revealed pulmonary hypertension with systolic pulmonary artery pressures ranging between 60 to 80 mm Hg. Right ventricular end-diastolic pressures were about 20 mm Hg. Cardiac index averaged 1.33 liters/min/m². Intravenous ouabain resulted in little change in right ventricular end-diastolic pressure. Systolic, diastolic, and mean pul-

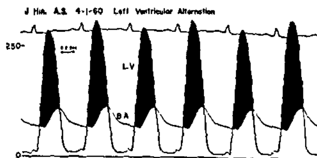


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Left heart catheterization is also of considerable value in the diagnosis of mitral stenosis in a select group of patients with very severe pulmonary hypertension; in these subjects, the murmur of mitral stenosis may be atypical in character or may even be absent. As described by Mackinnon et al. (1956), the physical signs are characteristic of severe pulmonary hypertension per se.

Cardiac catheterization techniques have been utilized to study coronary blood flow and myocardial oxygen consumption (Rowe et al, 1960). The results demonstrate a decrease in left ventricular coronary blood flow and a decrease in left ventricular oxygen consumption per unit weight of left ventricle.

Pulmonary blood volume, both total and true, as defined above, has been studied with cardiac catheterization techniques. Borden et al. (1949) first reported pulmonary artery to systemic artery volumes of 642 ml/m² in patients with rheumatic heart disease without signs of congestive heart failure. Lagerlof et al. (1949), Kopelman et al (1951), Doyle et al. (1953), Rapaport et al. (1956), and Milnor et al. (1960) reported corresponding values ranging between 817 to 887 ml/m². These values are only slightly larger than those observed in normal subjects. True *pulmonary* blood volume, i.e., the volume between the pulmonary artery and the left atrium, has been determined by Milnor et al. (1960) and by Dock et al. (1961). These studies revealed true pulmonary blood volumes between 322 to 365 ml/m².

Physiologic studies by right and combined heart catheterizations in patients with rheumatic aortic stenosis have revealed that left ventricular failure with elevation of the end-diastolic pressure is not infrequently seen, as noted above. It is of considerable interest that the cardiac index has been found to be within normal limits, or even somewhat elevated, by both direct Fick and indicator-dilution techniques in patients with severe aortic stenosis with overt left ventricular failure (Hancock and Fleming, 1960, Dexter et al., 1958). Left heart catheterization has also revealed that many of the clinical features of aortic stenosis may be noted in symptomatic patients who are being considered for aortic commissurotomy—but significant aortic stenosis may not be present, as determined by the absence of a systolic left ventricular–systemic arterial gradient of any magnitude (Hancock et al, 1958).

Unnecessary cardiac surgery may thus be obviated.

ARTERIOSCLEROTIC HEART DISEASE

Hemodynamic data in *acute myocardial infarction* have become available in the past 10 years

Freis et al. (1952) studied 11 patients with acute infarction *Cardiac output was measured by the indicator-dilution technique*, T 1824 was injected via a polyethylene tube passed into an axillary or subclavian vein and was sampled from the femoral artery Conditions of the patients were classified as (1) mild, (2) moderate and severe, and (3) with *cardiogenic shock* The second group exhibited signs of congestive failure The patients in the third group were severely ill, all eventually died In the first group, cardiac index was normal—mean, 3 4 liters/min/m², heart rate, 92, stroke volume, 76 ml beat, and central venous pressure, 90 mm water In the second group, cardiac index was 2 9 liters/min/m², heart rate, 101, stroke volume, 50, and central venous pressure, 120. In the third group, cardiac index was 1 8 liters/min/m², heart rate, 128, stroke volume, 27, and central venous pressure, 115. Central blood volume was similar in all three groups

Gilbert et al (1954) studied 20 patients with acute myocardial infarction by similar techniques. The first group (7 patients) exhibited neither heart failure nor shock, cardiac index was 2 61 liters/min/m², venous pressure was 130 mm water. The second group (6 subjects) was in cardiac failure, with an index of 1 9 liters/min/m² and a venous pressure of 167 mm water. All 7 subjects in the third group were *in shock, with a cardiac index* of 1 0 liters/min/m² and a venous pressure equal to 215 mm water

Smith et al (1954) made measurements of cardiac output in 9 patients with acute infarction without shock and in 6 *with shock Cardiac output* was again measured by intravenous indicator injection with peripheral arterial sampling In the patients without peripheral shock, cardiac index totaled 2 4 liters/min/m² After recovery, cardiac index increased significantly, *to 2 7. In the 6 patients* in shock, cardiac index was 1 65.

Gammill et al (1955) investigated 37 patients with acute infarction Cardiac output was determined by the *indicator-dilution technique* Cardiac index was 4 25 liters/min/m² in the *least severe* group, 3.21 in the intermediate group, and 2.93 in the most severe group. On restudy 4 weeks after recovery, cardiac output in the third group had risen to the values in the first two groups In those patients in shock, failure of peripheral vasomotor mechanism was not demonstrated

Lee (1957) analyzed *the data in* 11 patients with acute infarction, utilizing similar techniques for determination of cardiac output. Cardiac index was normal, 3.7 liters/min/m², even in those patients in *shock*. The most consistent hemodynamic observation in these patients was an *elevated venous pressure*.

Broch et al. (1959) studied 35 subjects with acute myocardial infarction. Those in group I (18 subjects) were uncomplicated, those in group II exhibited shock or failure. *Indicator-dilution techniques* with peripheral venous injection were employed The cardiac index *in the first group* was normal, 3 03 liters/min/m², this index was reduced to 2.04 in the second group Stroke volume changes followed output data. Eight patients in group II died, 9 survived The cardiac index in those that survived was 2.36, in the nonsurvivors *the index* was 1.73 On restudy 3 weeks after infarction, the *patients in group I exhibited* little change, while those in group II showed considerable improvement.

Cardiac dynamics in asymptomatic male patients with *healed myocardial infarction* were studied by *Chapman and Fraser (1954). The infarcts had* occurred at least 6 months before study. The cardiac index at rest was 2 95 liters/min/m². The increase in cardiac output during exercise was equivalent to that noted in a comparable group of normal subjects, indicating that a normal response to the stress of exercise could be expected in this type of subject

Lewis et al. (1953) catheterized three patients with arteriosclerotic heart disease and heart failure. Cardiac index at rest averaged 1.73 liters/min/m². Stroke volume per square meter averaged 21 ml. *Pulmonary artery wedge pressure (employed as an* indicator of mean left atrial pressure) was 32 mm Hg Pulmonary artery mean pressure was 44 mm Hg During moderate exercise (oxygen consumption rose from 133 to 198 ml/min/m²), cardiac *index rose to 1.9 liters/min/m²*; stroke index fell to 19 ml Pulmonary artery wedge pressure rose to 39 mm Hg, pulmonary artery mean pressure increased to 57 mm Hg Right atrial mean pressure data, obtained only at rest, averaged 18 mm Hg, *indicating that right as well as left heart failure* was present.

Bloomfield et al (1948) studied the effect of intravenous *ouabain* in three patients with arteriosclerotic heart disease in failure. Control *measurements revealed* pulmonary hypertension with systolic pulmonary artery pressures ranging between 60 to 80 mm Hg. Right ventricular *end-diastolic* pressures were about 20 mm Hg Cardiac index averaged 1.33 liters/min/m² Intravenous ouabain *resulted in little* change in right ventricular end-diastolic pressure. Systolic, diastolic, and mean pul-

monary artery pressures rose within 1 hr. Cardiac output rose to about 2.1 liters/min/m². These responses are compatible with the effect of increased flow upon a restricted pulmonary bed. Judson et al. (1955a) catheterized two patients with arteriosclerotic heart disease, one in failure, one in cardiac compensation. In the latter subject, right ventricular end-diastolic pressures remained normal at rest and during exercise; pulmonary artery wedge pressure was elevated only during exercise, suggesting the development of left heart failure. Cardiac index was diminished at rest (1.95 liters/min/m²) and rose subnormally (relative to the increase in oxygen consumption) during exercise. The minimal pulmonary hypertension at rest rose markedly during exercise. In the decompensated subject, right ventricular end-diastolic pressure was markedly elevated at rest and rose further during exercise. Moderately severe pulmonary hypertension was observed at rest and rose further during exercise. The cardiac index at rest was 2.10 and rose subnormally during exercise

Hemodynamic studies during episodes of *precordial pain* have been reported by Muller and Rorvik (1958) Eleven subjects had previous myocardial infarction; precordial pain was the predominant symptom. Observations at rest showed elevation of the pulmonary artery wedge pressure in only 1 subject. Mean pulmonary artery pressure was minimally elevated in 3 subjects; cardiac index was normal During *bicycle exercise* in the recumbent position, 7 of 8 patients developed precordial pain Exercise elevations in mean pulmonary artery and wedge pressures were common. Cardiac output rose normally during exercise Three patients with pain but without recognized infarction were investigated Normal resting hemodynamics were noted, during exercise, significant increments in wedge and pulmonary artery pressures were observed Two patients developed spontaneous precordial pain during catheterization. Control hemodynamics were normal During the episode of pain, marked elevation of wedge pressure occurred. Eight patients complained of *exertional dyspnea* without pain. Cardiac enlargement was present in all, cardiac index was normal in 6 Pulmonary artery and wedge pressures were elevated at rest and rose further during exercise In 4 additional patients, *nitroglycerin* administration prevented an exercise elevation in pulmonary artery wedge pressure.

Gorlin et al. (1959a) and Brachfeld et al (1959) investigated the action of *nitroglycerin* on the coronary circulation and on right and left heart hemodynamics. In normal subjects and in those with "mild" cardiac disease (with a small atrial defect and a grade 1 basal diastolic murmur), nitroglycerin caused no change in cardiac output, and pulmonary artery and wedge pressures fell slightly. Brachial artery pressure decreased minimally. Coronary artery blood flow and oxygen consumption per 100 Gm of left ventricular muscle increased 63 per cent after administration of *nitroglycerin*. On the other hand, in patients with coronary artery disease or increased left ventricular work (mitral insufficiency, aortic valve disease, or both), nitroglycerin administration resulted in a 15 per cent fall in cardiac index. Brachial artery, pulmonary artery, and pulmonary artery wedge pressure fell 15, 50, and 50 per cent, respectively. Coronary blood flow and oxygen consumption either fell slightly or remained unchanged. A concept of "fixed" coronary blood flow was suggested to explain the latter results in patients with coronary artery disease and increased left ventricular work.

Selzer (1959 and 1960) has investigated the hemodynamic consequences of arteriosclerotic heart disease after therapy for, and recovery from, clinical left heart failure. Left atrial mean pressure was measured as mean pulmonary artery wedge pressure The conditions of the patients studied fell into four categories (1) normal resting dynamics with *abnormal* response to exercise, i.e., the *development of* pulmonary artery hypertension during exercise, (2) normal resting left atrial pressure with a low resting cardiac output, (3) elevated left atrial pressure with a normal cardiac output at rest, (4) elevated left atrial and pulmonary artery mean pressures and a low cardiac output at rest. Marked similarities and only minor differences were observed between the hemodynamic changes caused by elevation of the left atrial pressure in mitral stenosis and those caused by chronic left ventricular failure.

Sobol et al (1959) evaluated the effect of induced peripheral vasodilatation (with *Arfonad*) in 4 patients with arteriosclerotic heart disease in failure Control data revealed marked reduction in cardiac index with elevation of pulmonary artery and wedge pressure and right ventricular end-diastolic pressure. Peripheral vasodilatation resulted in an increase in cardiac index with a decrease in pulmonary artery and right ventricular pressures.

... (1960) and Eisenberg et

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to moderate heart failure, cerebral blood flow and oxygen consumption were normal despite a significant increase in cerebral vascular resistance. In severe heart failure, cerebral blood flow and oxygen consumption were both significantly decreased. In advanced heart failure in confused subjects, further marked decreases were observed in the latter two parameters.

HYPERTENSIVE HEART DISEASE

The development of effective depressor therapy for essential hypertension has led to detailed hemodynamic studies in patients with this disease. Cardiac index and right heart pressures are normal in the patient not in failure (Varnauskas, 1955; Goldring and Chasis, 1944). Left heart catheterization data are not available. Ganglionic-blocking agents, guanethidine, and bretylium, all produced decrease in cardiac output as part of the hypotensive mechanism noted with these agents. Chlorothiazide administration also results in a decrease in cardiac output during initiation of therapy (Conway and Lauwers, 1960; Crosley et al., 1958; Dustan et al., 1959). Conway and Lauwers (1960) have shown, however, that more prolonged chlorothiazide administration is not associated with a reduction in output.

Hemodynamic data in left ventricular failure have been reported. Werko and Lagerlof (1949) were the first to report elevation of pulmonary artery wedge pressure in hypertensive subjects, suggesting left heart failure. Harvey et al. (1949) reported 3 patients with pure left ventricular failure secondary to systemic arterial hypertension. Pulmonary artery pressure was elevated in all 3; right ventricular end-diastolic pressures were normal. Cardiac index was normal in 1, low normal in 1, and reduced in the third. After administration of

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changed. These studies demonstrated that the initial action of digoxin was directly exerted on ...

... upon the enlarged hypertensive heart of 2 patients not in failure at the time of study.

Right ventricular end-diastolic pressure remained unchanged, but cardiac index fell significantly. The decreases in output in 3 subjects with arteriosclerotic heart disease not in failure were of lesser magnitude.

Johnson et al. (1957) catheterized 6 patients with hypertensive heart disease and right and left heart failure before and after sublingual nitroglycerin administration. The control elevated mean pulmonary artery pressure fell 10 mm Hg; a simultaneous fall in systemic arterial pressure was observed. No correlation could be established between the decreases of pressure in the two arterial trees. In two instances, pulmonary artery wedge pressure was also measured; this value was elevated and fell after nitroglycerin administration, suggesting a decrease in left atrial pressure. Cardiac output data were not available. The mechanism of the fall in pulmonary artery pressure is, therefore, not clear.

Ferrer et al. (1960) reported studies in subjects with hypertensive heart disease suffering from right and left heart failure. Four patients had sinus rhythm. Control measurements revealed low cardiac indexes, moderate to severe pulmonary hypertension, and elevation of right ventricular end-diastolic pressure. Intracardiac digoxin resulted in a rise of cardiac index, and a fall of pulmonary artery and right ventricular pressures. In one patient, the increase of cardiac output was associated with a rise of pulmonary artery pulse pressure. In two patients, the rhythm was atrial fibrillation. Digitalization resulted in hemodynamic changes similar to those observed in patients with sinus rhythm. The control data in the patients with atrial fibrillation revealed more marked reduction of cardiac index and considerably less pulmonary hypertension than in those with sinus rhythm.

Detailed analysis of the interrelationships between the varied hemodynamic responses to acute digitalization, i.e., changes in heart rate, cardiac output, and right heart pressures, revealed that changes in these parameters did not necessarily occur simultaneously. Increments in cardiac index could precede changes in right heart pressures or vice versa. No constant relationship could be established between a fall in heart rate and alterations of right heart pressure or changes of cardiac index.

The data in this study thus emphasize the concept that digitalization may result in clinical and hemodynamic improvement without

immediate rate changes. The implication of this concept in the clinical use of digitalis is obvious. The results of Ferrer's study also illustrate that *significant clinical and hemodynamic improvement may follow relatively small doses of digoxin.* Results of similar studies in which left atrial and left ventricular pressure data are also available will be awaited with great interest. These hemodynamic alterations following digitalization in patients with hypertensive heart disease were also observed in patients in combined right and left heart failure caused by arteriosclerotic heart disease.

The catheterization studies in patients in heart failure by Bloomfield et al (1948), Lewis et al. (1953), Selzer (1959), Selzer and McCaughey (1960), and Sobol, Eichna, et al. (1959) also included persons with hypertensive heart disease. The results were similar to those noted in patients with arteriosclerotic heart disease in failure.

Judson *et al* (1955b) investigated the hemodynamic effects of *venous congestion* or of *phlebotomy* in patients with hypertensive heart disease with and without heart failure.

Cardiac index data are not available. In the 3 subjects not in failure, right heart pressures were normal. After venous congestion, cardiac output fell more than 10 per cent Right heart pressures were unchanged. In the 4 subjects in heart failure, moderate to severe pulmonary artery hypertension was recorded with elevation of the right ventricular end-diastolic pressure. Venous congestion in three subjects resulted in a slight increase in cardiac output and a fall in right ventricular end-diastolic pressure and pulmonary artery pressure. Phlebotomy produced a similar result in the fourth subject.

Donald (1959a) and Taylor (1957) reported data on circulatory studies in hypertensive patients studied at rest and during exercise.

Twenty subjects were studied Thirteen subjects in group I were free of marked left ventricular enlargement or dyspnea Seven subjects in group II had severe exertional dyspnea. The patients in group I exhibited normal cardiac indexes and pulmonary artery and wedge pressures at rest. During exercise, cardiac output rose normally, but an increase in wedge pressure was commonly observed. In group II, cardiac indexes were often but not invariably decreased at rest. Wedge pressures were elevated in some instances but not in all. During exercise, all patients in group II showed an impairment of the cardiac output response and a rise of wedge pressure. It is of considerable interest that the electrocardiographic demonstration of left ventricular hypertrophy did not necessarily imply hemodynamic abnormality. A number of patients with this electrocardiographic pattern showed normal hemodynamics both at rest and during exercise. One patient with a normal electrocardiogram, on the other hand, exhibited abnormal hemodynamic data.

COR PULMONALE

Hemodynamic studies in cor pulmonale (heart disease secondary to diseases of the lung) with and without congestive heart failure have provided considerable background of the pathophysiology of this disease. A lively discussion has ensued as to the cardiac output in cor pulmonale due to obstructive pulmonary emphysema. Several authors have reported that *the cardiac index in obstructive pulmonary emphysema with cor pulmonale is higher than in patients with valvular, hypertensive, or arteriosclerotic heart disease, and may be normal or even higher than normal.* However, other studies have presented conflicting results, in that *the cardiac index was normal or decreased in these patient*

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normal in chronic cor pulmonale secondary to *obstructive emphysema*—at least in Mounsey's series. The high cardiac index noted in Mounsey's patients was *secondary* to the high resting oxygen consumption. The normal arteriovenous difference in these patients was contrasted with the lower-than-normal arteriovenous difference observed in the high-output failure of severe anemia and systemic arteriovenous fistula.

Other investigators have tried to relate the level of cardiac output to the arterial oxygen saturation. Arterial hypoxemia has been postulated to be at least one of the mechanisms of the elevated cardiac index observed in some subjects Whatever the initial level of cardiac output in patients with cor pulmonale due to emphysema in heart failure, there is considerable evidence that as such patients recover from failure, a decrease in output takes place.

Coronary blood flow in pulmonary emphysema and cor pulmonale (Rose et al., 1956) 113

is within the normal range. In one patient with an elevated cardiac index, coronary blood flow was also elevated.

Cor pulmonale due to obstructive *emphysema is often associated with some degree of pulmonary hypertension*, either at rest or during exercise Arterial oxygen unsaturation below 80 per cent, hypercarbia, increased cardiac index, increased total blood volume, and restriction of the *pulmonary vascular bed, either* structural or vasoconstrictive, are some of the factors that have been suggested as causing or contributing to pulmonary hypertension (Fishman and Richards, 1956, McMichael, 1959).

Slight to moderate pulmonary hypertension with elevation of right ventricular end-diastolic pressure is commonly observed in the decompensated state Acute digitalization results in *an increase of cardiac output and a decrease of right ventricular end-diastolic pressure,* but in contrast to the findings in pure left ventricular failure, *a further rise developed in pulmonary artery pressure.* The increase of pulmonary artery pressure under such circumstances is probably due to the effect of an increase of cardiac output in the presence of a restricted pulmonary vascular bed Restudy weeks to months after the first catheterization revealed marked decrease of pulmonary artery pressure to normal or slightly elevated levels, right ventricular end-diastolic pressure had returned to normal *Of considerable interest* was the decrease of cardiac output at this time compared to the acute studies in heart failure (Ferrer et al, 1950, Özcan et al, 1951). Digitalization in patients with obstructive emphysema *not in failure* produced none of these changes.

Exercise studies in obstructive emphysema, with or without cor pulmonale, usually show elevation of pulmonary artery pressure if it was initially normal, or a further elevation if it was initially *elevated*. Cardiac output data are limited (Ferrer and Harvey, 1959, Hickam and Cargill, 1948) In some instances, blood flow rises normally during exercise with a rise in right ventricular end-diastolic pressure, in more severe cases, there is little or no rise in output despite a further *increase in right* ventricular end-diastolic pressure.

Kyphoscoliosis may also be associated with cor pulmonale and heart failure (Bergofsky et al., 1959, Fishman et al, 1956a)

Cardiac index was normal in 13 patients with kyphoscoliosis at rest. None was in *failure. Pulmonary hypertension was present* in 5 subjects at *rest* During exercise, abnormal increments were observed in pulmonary artery pressure in all instances. The exercise increase of cardiac index was normal.

The mechanism of cor pulmonale in these subjects is *chest deformity resulting in an increased work of breathing, alveolar hypoventilation, hypercapnea, hypoxemia, and pulmonary hypertension.* In the above forms of cor pulmonale, pulmonary artery wedge pressure is normal both at rest and during exercise, indicating that pulmonary artery hypertension is caused by increased resistance to flow in the pulmonary vascular bed at a point proximal to the left atrium.

Unlike the findings in cor pulmonale with obstructive emphysema, cardiovascular dynamics in patients with *diffusion block* (Harvey et al., 1951b) are characterized by pulmonary hypertension at rest and a considerable increase in cardiac index (mean, 3.99 liters/min/m²) in the presence of a normal hematocrit. Pulmo*nary hypertension may be present before* significant hypoxemia develops at rest. In these subjects, pulmonary hypertension appears to be caused by anatomic restriction of the vascular bed, rather than by the diverse physiologic factors operative in pulmonary emphysema.

Demonstration of the enlargement of the *bronchial arterial tree in bronchiectasis* (Liebow et al., 1949) has aroused interest in measurement of the bronchial arterial flow by simultaneous estimation of right and left ventricular outputs (Cudkowicz et al, 1959, Nakamura et al., 1961) and by simultaneous cardiac *catheterization*, bronchospirometry, and unilateral *pulmonary artery occlusion* (*Fishman* et al, 1958).

CONSTRICTIVE PERICARDITIS

Some of the varied hemodynamic patterns *that develop in* pericardial disease have been outlined by *Harvey et al. (1953)* Mechanical and myocardial factors in *chronic constrictive* pericarditis were differentiated.

One patient of Harvey's series presented the classic clinical and hemodynamic patterns of *constrictive* pericarditis. Mild pulmonary *hypertension was present*, with a narrowed pulse pressure, *systolic pulmonary* artery pressure was only minimally elevated in the face

of disproportionate elevation of the diastolic and mean pulmonary artery pressures. Right ventricular end-diastolic pressure was markedly elevated, with the typical early-diastolic dip rising to a diastolic plateau (Fig. 18-15). Cardiac index was slightly reduced. These hemodynamic abnormalities, due predominantly to a thickened, poorly distensible pericardium, had completely disappeared 3 months after surgery. A second patient exhibited the same classic hemodynamic findings of constrictive pericarditis but had a normal cardiac index in the absence of clinical signs or symptoms of this disease. A third patient demonstrated that extensive *pericardial calcification* may exist in the absence of hemodynamic or clinical cardiac abnormalities, at least at rest. The fourth subject exhibited a marked reduction in cardiac index, associated with a narrowed pulmonary artery pulse pressure, a high diastolic pressure, and a slightly elevated systolic pressure. Right ventricular end-diastolic pressure was markedly elevated. After acute digitalization during catheterization, cardiac output rose, with a fall in pulmonary artery and right ventricular pressures. This response suggested a failing myocardium in this patient with constrictive pericarditis. The fifth subject showed a normal cardiac output but with right ventricular and pulmonary artery pressure curves characteristic of constrictive pericarditis. After 1 month of intensive therapy, restudy revealed considerable diminution of the hemodynamic signs of constrictive pericarditis. These alterations rendered the concept of the mechanical interference of pericardial constriction per se untenable. The pathogenesis of the hemodynamic abnormalities in this last case remained unclear.

Hansen et al. (1951) have published similar data illustrating the typical *early-diastolic dip* in the right atrial and ventricular curves. These dips disappeared after pericardiectomy. Murphy et al. (1958) studied 6 patients with *constrictive pericarditis*. Cardiac indexes varied from markedly reduced levels to normal levels. Right atrial and right ventricular end-diastolic pressures were typically elevated, as were pulmonary artery pressures. Pulmonary artery wedge pressures were also increased. On exercise, further increases were noted in right heart pressures. In 3 cases, right heart pressures were normal during rest and exercise after surgery.

Wilson et al. (1954) have reported similar data in 10 patients with constrictive pericarditis. A right ventricular diastolic dip was present in all patients, together with marked elevation of the right ventricular end-diastolic pressure. A small pulmonary artery pulse pressure was noted. Identical hemodynamic abnormalities were observed in 3 patients with *pericardial effusion*. Wilson stated that the right ventricular diastolic to systolic pressure ratio was greater than 40 per cent in constrictive pericarditis.

It must be emphasized that although the above hemodynamic abnormalities are highly characteristic of constrictive pericarditis, they are not pathognomonic thereof. Balchum et al. (1956) and Clark et al. (1956) have emphasized that patients with *endocardial fibrosis* and *nonspecific myocarditis* may exhibit identical abnormalities.

HIGH-OUTPUT FAILURE

Cardiac failure associated with the high-output state has evoked considerable interest. Most cases have been associated with systemic arteriovenous fistulas, anemia, beriberi, and hyperthyroidism. Reduced resistance to outflow of blood from the systemic arterial tree is common to these conditions (Youmans, 1957).

Gorlin et al. (1959b) have described a group of 8 subjects with a persistently elevated *cardiac output* associated with cardiac *hypertrophy* and a precordial systolic murmur. The average cardiac index was 6.4 liters/min/m². The average oxygen consumption was 177 ml/min/m², a figure considerably higher than the basal level of about 125 to 135 ml/min/m². The arteriovenous difference was 2.8 vol per cent, a figure comparable to the levels seen in anemia and systemic fistulas with failure. The resting heart rate of 79 suggests that anxiety was not the cause of the elevation in cardiac output. The stroke index was therefore *increased* to 80 ml/beat/m². The response to exercise was unusual, however, in that *cardiac output* remained unchanged despite an increase in oxygen consumption. The etiology of these unusual hemodynamic findings is uncertain.

Perhaps the most typical example of *high-output failure* is seen in patients *with systemic arteriovenous fistulas*.

Cardiac index was elevated in 4 of 6 patients studied by Epstein et al. (1953); the actual values varied from 4.16 to 5.15 liters/min/m². The index fell considerably during occlusion of the fistula. In 2 subjects, the index was normal and did not

change during occlusion of the fistula. The latter procedure resulted in the expected increase in arterial pressure and slowing of the pulse in all 6 subjects

Muenster et al. (1959) studied 6 patients with fistulas, 2 with overt congestive failure.

Right atrial mean pressure was markedly elevated to 20 mm Hg in the last two. Cardiac index was markedly elevated (4.84 to 8.86) in all patients. Oxygen consumption ranged from 125 to 171 ml/min/m². Arteriovenous differences were depressed and ranged from 1.86 to 2.87 vol per cent. Exercise produced an increase in output in the 4 subjects not in failure. In the 2 subjects in failure, output fell during exercise. Mean pulmonary artery pressure was elevated in all 6 subjects at rest and rose further during exercise.

Bishop et al. (1955) reported similar data in 2 patients with systemic arteriovenous fistulas, viz., an increased cardiac index, decreased arteriovenous difference, and normal oxygen consumption. Pulmonary artery mean pressure was slightly elevated in both. Bishop also reported 11 patients with severe anemia; in 8 subjects the hemoglobin was below 6 Gm/100 ml. Cardiac index was elevated in all, oxygen consumption was normal, and arteriovenous oxygen difference was decreased. Mean pulmonary artery pressure was normal or slightly elevated. Five patients with hyperthyroidism were catheterized by Bishop et al. All had elevated cardiac indexes and oxygen uptakes. Arteriovenous differences were depressed. Pulmonary artery mean pressures were slightly elevated.

Similar data in hyperthyroidism has been reported by Humerfelt et al. (1958), Rowe et al. (1956), and Leight et al. (1956). Humerfelt noted an average cardiac index of 6.1 liters/min/m² in 32 patients. The arteriovenous difference was slightly reduced. Right heart pressures were normal. After therapy, in 16 patients, cardiac index and oxygen consumption fell proportionately so that the arteriovenous differences remained normal. Pulmonary artery pressures decreased slightly after therapy. Rowe's data were similar except for the frequent observation of a normal arteriovenous difference. This investigator also reported that coronary blood flow and ventricular oxygen uptake rose in thyrotoxicosis. Leight has also reported an increased mean coronary blood flow and oxygen consumption in hyperthyroidism.

Blacket et al. (1960) reported hemodynamic observations in 16 patients with heart disease due to thiamine deficiency. Cardiac index varied between 4.2 and 15.5 liters/min/m². Mean oxygen consumption was slightly elevated to 156. Arteriovenous oxygen difference was considerably decreased. Right heart pressures varied considerably. Elevated right atrial mean and right ventricular end-diastolic pressures were observed frequently.

High-output failure has also been reported in Paget's disease. Howarth (1953) investigated 13 cases. In 12 patients with active disease, cardiac output was increased in the 5 in whom study revealed 35 or more per cent skeletal involvement, or more, and plasma alkaline phosphatase levels of more than 45 King-Armstrong units. Arteriovenous oxygen difference was low in these 5 cases, indicating a true high-output state.

HEMODYNAMIC STUDIES IN ATRIAL ARRYTHMIAS

The clinical frequency of atrial fibrillation and atrial flutter has evoked interest in the hemodynamic consequences of these arrythmias. Most studies have demonstrated a rise in resting cardiac output after conversion from atrial fibrillation to sinus rhythm.

Hanssen et al. (1952) studied 14 patients, both at rest and during exercise, during atrial fibrillation and sinus rhythm. Measurements at rest revealed a rise in cardiac output after conversion to sinus rhythm in 9 patients; in 6 of these 9, the cardiac index rose to a normal resting level. In 5 of the 12 patients who were exercised while the rhythm was atrial fibrillation, there was a significant increase in cardiac output over the resting value. The average rise was 18 per cent in the 9 patients who demonstrated an increase in output over the resting value. After conversion to sinus rhythm, 11 of the 12 patients increased their output during exercise as compared to the resting value. In general, therefore, conversion to sinus rhythm resulted in a rise in cardiac output.

Broch and Muller (1957) studied 20 patients before and after conversion to sinus rhythm. Cardiac output and stroke volume increased both at rest and during exercise after restoration of sinus rhythm. Pulmonary artery pressure was unchanged by conversion, but wedge pressure rose after conversion, both at rest and during exercise. Kory and Meneely

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Cardiac failure associated with the high-output state has evoked considerable interest Most cases have been associated with systemic arteriovenous fistulas, anemia, beriberi, and hyperthyroidism. Reduced resistance to outflow of blood from the systemic arterial tree is common to these conditions (Youmans, 1957).

Gorlin et al (1959b) have described a group of 8 subjects with a persistently elevated cardiac output associated with cardiac hypertrophy *and a precordial systolic murmur*. The average *cardiac index* was 6.4 liters/min/m^2. The average oxygen consumption was 177 ml/min/m^2, a figure considerably higher than the basal level of about 125 to 135 ml/min/m^2. The arteriovenous difference was 2.8 vol per cent, a figure comparable to the levels seen in anemia and systemic fistulas with failure. The resting heart rate of 79 suggests that anxiety was not the cause of the elevation in cardiac output. The stroke index was therefore *increased* to 80 ml/beat/m^2. The response *to exercise* was unusual, however, in that cardiac output remained unchanged despite an increase in oxygen consumption. The etiology of these unusual hemodynamic findings is uncertain

Perhaps the most typical example of high-output failure is seen in patients with *systemic arteriovenous fistulas*

Cardiac *index* was *elevated* in 4 of 6 patients studied by Epstein et al. (1953), the actual values varied from 4 16 to 5.15 liters/min/m^2. The index fell considerably during occlusion of the fistula. In 2 subjects, the index was normal and did *not*

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Treatment of heart failure

SIMON DACK

With better understanding of the myocardial and hemodynamic disturbances associated with heart failure, the treatment of this condition has become increasingly effective.

In previous chapters, it has been shown that the clinical manifestations of failure result primarily from a decrease in cardiac output to a level inadequate for the metabolic needs of the body, and secondarily from renal retention of salt and water, producing increased blood volume and edema in the lungs, viscera, and peripheral regions The latter is a result of the reduced renal blood flow, diminished glomerular filtration, and tubular dysfunction secondary to the reduced cardiac output To be effective, treatment must either improve myocardial function and increase cardiac output, or improve renal function (by affecting either the vascular or the tubular function), thereby producing diuresis of salt and water and eliminating edema Often it is difficult to dissociate the cardiac and renal effects of a procedure or drug.

The therapeutic measures presently available are directed, respectively, at (1) removing or alleviating the intrinsic cardiovascular lesions responsible for cardiac failure, i.e., eliminating the cause, (2) improving the state of the myocardium so that cardiac function and circulatory dynamics are restored to normal or improved, (3) reducing the work of the heart and protecting it from the effects of increased work and strain, and (4) eliminating edema fluid resulting from renal disturbance secondary to the heart failure

BASIC PRINCIPLES OF TREATMENT

The basic principles of treatment for heart failure are (1) to improve myocardial efficiency and increase cardiac output, (2) to reduce venous congestion and edema by dietary salt restriction and diuretic therapy aimed at decreasing reabsorption of sodium and water.

The following therapeutic measures, which comprise the basis of the modern therapy of heart failure, will be discussed: rest; dietary regulation of salt intake, digitalization; diuretic therapy, and ancillary measures to improve cardiac function (oxygen, antibiotics, anticoagulants, steroids, vitamin therapy, etc.).

Importance of Precipitating Factors of Heart Failure. It must be emphasized that in most cases of heart failure, there is an acute precipitating cause for the failure in addition to the underlying cardiac disease. These precipitating causes are (1) infection, generally pulmonary or associated with a bacteremia, (2) tachycardia or cardiac arrhythmia with excessively rapid or slow ventricular rate; (3) strain produced by physical or emotional stress, (4) overloading of the circulation by excessive dietary salt and fluid intake or following parenteral administration of saline solutions; (5) acute myocardial damage by inflammation, toxins, or infarction, (6) progressive impairment of myocardial function by recurrent carditis, ischemia, necrosis, or dilatation, (7) mechanical disturbances, such as those induced by pericarditis and pericardial effusion; (8) improper or inadequate previous therapy, including underdigitalization, overdigitalization, inadequate diuretic therapy, and (9) electrolyte disturbances due to advanced failure and excessive electrolyte loss by diuresis.

A search for these possible precipitating causes is mandatory in every patient, since successful management depends on the recognition and treatment of such correctible intrinsic

(1951) reported similar changes in 6 of 8 patients after restoration of sinus rhythm. Hecht et al. (1951 and 1956) studied 15 patients. While at rest, the mean increase of cardiac output after conversion to sinus rhythm was small but the exercise increase was statistically significant. Pulmonary artery pressure remained unchanged.

Harvey et al. (1955a) catheterized 8 patients with atrial flutter with heart disease of varying causes. Cardiac output was generally low. Pulmonary hypertension of varying magnitude was noted in those in heart failure. Conversion to sinus rhythm in 5 patients resulted in a 40 per cent rise in cardiac output at rest, while oxygen consumption remained unchanged. In 2 patients the response to exercise during flutter was similar to that after conversion to sinus rhythm

Mahrer et al. (1957) reported data in a patient who developed *atrial flutter* during cardiac catheterization and then reverted spontaneously to sinus rhythm during the course of the catheterization. The ventricular rate was the same during both rhythms. Neither cardiac output nor right heart pressure levels were altered by atrial flutter, although exact comparison is made difficult by the fact that the oxygen consumption (ml/min/m^2) was 153 and 131 during atrial flutter and sinus rhythm, respectively.

SUMMARY

The hemodynamic consequences of heart failure in varied types of heart disease have been outlined. *Elevation of the right or left ventricular end-diastolic pressure and of the atrial mean pressure* has been suggested as the initial hemodynamic manifestation of such failure. Changes in cardiac output are generally noted. Congestion of the venous bed behind the failing ventricle eventually follows. The concept of noncardiac circulatory congestion has been discussed by Eichna (1960). The eventual place of this concept in cardiovascular physiology remains to be evaluated.

duce the renal blood flow and increase edema formation. On the other hand, the greater renal blood flow in the horizontal position makes it desirable for the patient to rest in bed for several hours after a mercurial injection in order to increase the diuretic response.

2. In the sitting position, dyspnea and orthopnea are lessened. In fact, the patient with pulmonary congestion may find it impossible to be flat and is comfortable only when propped up in bed or sitting in a chair. The gravity effect of the upright position results in increased drainage of fluid from the lungs and pleural cavities and improved pulmonary ventilation.

3 Body position is a factor in determining the site of edema accumulation. During the day, with the patient in the sitting or upright position, edema tends to occur in the lower and dependent portions of the body At night, however, if the patient resumes the recumbent position in bed, the increased venous return to the right heart may increase the blood flow to the lungs and precipitate acute pulmonary congestion or edema Similarly, overloading of the pulmonary circulation may occur when complete rest in bed is suddenly imposed on patients with long-standing right heart failure and persistent peripheral edema, who have been out of bed or ambulatory.

In the clinical management of patients with heart failure, one must weigh the possible good and bad effects of enforced bed rest. Patients with dyspnea and orthopnea due to acute left heart failure are put to bed and propped up with pillows and back rests as high as is consistent with comfort, but as soon as feasible they should be allowed to sit up in a chair for increasing periods In cases where the patient is kept in bed for long periods, the measures outlined in Part 19, Chap. 3 should be carried out to prevent peripheral venous stasis and thromboembolism (encouraging movement of lower limbs, elastic bandaging of the legs, anticoagulant therapy, care of bowel function, use of bedside commode, etc)

DIETARY REGULATION OF SALT INTAKE

Despite the availability of potent diuretics to increase the excretion of excess sodium, regulation of dietary sodium intake remains an important part of the management of failure. (A more complete discussion of this subject is given in Part 19, Chap. 5.) An adequate clinical response to diuretic and digitalis therapy depends upon restriction of salt intake to a level which the kidneys can handle. It has been claimed that there is a direct linear proportion between dietary salt intake, urinary sodium excretion, and response to diuretic agents.

The degree of dietary salt restriction required must be individualized in each case and is dependent on the severity and progression of the congestive symptoms and edema. Severe sodium restriction to 500 to 800 mg daily is generally necessary in acute failure or in chronic failure with massive edema. This will generally increase the saluretic response to diuretic therapy and permit reduction in dosage and frequency of administration, minimizing the danger of toxic effects. In patients with a moderate degree of failure, particularly after the edema has disappeared, the salt intake can be more liberal Such patients may be kept edema-free with only mild to moderate salt restriction (abstention from salty foods, and eliminating salt in the cooking and the salt shaker at the table), supplemented with a daily oral thiazide derivative, and occasional mercurial injection if necessary. In patients with only mild heart failure, or those who have completely recovered from acute failure, only slight limitation of salt intake is necessary. The trend in recent years has been to be more liberal with salt intake in such patients, provided maintenance therapy with digitalis and the potent oral diuretics is continued. This may obviate the necessity for prolonged salt restriction Close observation for detection of recurrent edema is indicated to determine the necessity of resuming restriction of salt intake.

DIGITALIS THERAPY

Digitalis is the most important drug in the treatment of heart failure.

Its clinical use is based on the following physiologic actions:[1]

1 The vagal stimulating effect depresses conduction through the AV conduction system. This results in slowing of the ventricular response when atrial arrhythmias (flutter and fibrillation) are associated with congestive failure. Similarly, the vagal stimulation may depress the SA node and slow the heart rate in the presence of normal sinus rhythm, but this effect is not significant

[1] See Part 21, Chap 10. *Editor.*

and extracardiac factors. In addition, other predisposing causes of heart failure that may require treatment should be looked for, such as hyperthyroidism, hypothyroidism, vitamin B deficiency, pulmonary embolism, extra- or intracardiac shunts, and other cardiovascular lesions amenable to surgery such as valvular or infundibular stenosis, constrictive pericarditis, etc. It is evident that no form of treatment will be completely successful unless these predisposing causes are recognized and alleviated.

Factors Determining Response to Therapy. The cardiac reserve is determined by the type and duration of the heart disease, the severity of the complications and precipitating factors, and the response to therapy. Depending on these factors, cardiac reserve may be restored to its original state following recovery from heart failure or the patient may be left with a diminished reserve. With repeated bouts of failure, the cardiac reserve may progressively diminish and the patient may lapse into a state of chronic persistent failure.

The response to therapy, therefore, determines the degree of cardiac reserve of the patient, for when he is first seen, the manifestations of failure may be the same regardless of the stage of his heart disease. The response to therapy is obviously better in the early stages of heart disease than in the terminal stages Therefore, a good response to therapy (good cardiac reserve) determines the prognosis for each patient. The basic aim in treatment should be to restore myocardial efficiency and cardiac reserve to a maximal degree so that the patient can resume an ambulatory status and carry on his everyday activities This is generally attainable in patients with initial bouts of failure or when there are precipitating factors that can be recognized and controlled

REST

Physical activity may produce several deleterious effects on the patient with cardiac failure. (1) oxygen consumption, heart rate, cardiac output, and cardiac work are increased; (2) myocardial oxygen consumption is increased and myocardial hypoxia may occur in the hypertrophied, dilated, or ischemic heart, (3) renal blood flow and glomerular filtration are reduced during exercise, resulting in increased salt and water retention. For these reasons, cardiac failure may be precipitated or aggravated during physical effort or emotional stress. On the other hand, in the resting state, the oxygen consumption and circulatory and metabolic needs of the body are reduced, so that the failing heart, even with its reduced output, can better meet the circulatory requirements of the body. Furthermore, the renal blood flow is improved in the resting state in the supine position, resulting in increased glomerular filtration and diuresis of salt and water.

These considerations make it desirable to impose some degree of physical and emotional rest on all patients with heart failure so as to minimize the demands on the cardiovascular system. The degree of restriction of activity must be individualized in each case, depending on the severity of the underlying cardiovascular damage and heart failure. It may vary from a modification of the daily mode of life in mild cases (shorter work hours, frequent rest periods, avoidance of fatiguing travel) to complete bed rest and avoidance of all physical activity in severe cases. In cases of mild failure with impaired exercise tolerance, a short period of confinement to the home or hospital room may be desirable, with activities limited to chair rest and bathroom privileges. In more severe cases, a longer period of complete rest in bed or chair is necessary, and walking is avoided until the signs of failure disappear. This period may range from several days to several weeks or months. In such cases, the possible dangers of prolonged immobilization in bed should be considered.

Posture: Bed vs. Chair Rest. In Chap 3 of Part 19 it will be pointed out that prolonged immobilization in bed in the horizontal position may produce deleterious cardiopulmonary effects, and that dyspnea and orthopnea may improve sooner when the patient with cardiac failure is allowed to sit up in a chair. It was emphasized that body position plays an important role in the circulatory effects of rest. In the normal person, cardiac output is increased in the horizontal position, because of increased venous return to the heart, and is reduced in the sitting posture, because of decreased venous return. Although this physiologic adjustment is less marked in the cardiac patient, it may be associated with beneficial as well as deleterious effects during heart failure

1. Since the physiologic and metabolic demands on the heart are less in the sitting position than during recumbency, the work of the heart is diminished. However, the reduced cardiac output in the sitting position may re-

TABLE 18-21. CHARACTERISTICS OF THE DIGITALIS GLYCOSIDES

Digitalis glycosides	Commercial preparation and manufacturer	Onset of action	Peak effect, hr	Marked regression	Complete disappearance of effect, days
Administered intravenously:					
Strophanthin G	Ouabain (Arnaud)	5 min	½-2	10 hr	1-1½
Deslanoside	Cedilanid D (Sandoz)	15 min	1-2	24 hr	2-5
Digoxin	Lanoxin (B and W.)	15 min	1½-5	10 hr	3-5
Digitoxin	Digitaline Nativelle	15-30 min	6-8	2 days	10-14
Acetyl-digitoxin	Acylanid (Sandoz)	15-30 min	5-6	2 days	7-10
Administered orally:					
Digoxin	Lanoxin (B and W.)	1-3 hr	6	18 hr	5-7
Gitalin	Gitaligin (White)	2-4 hr	8-10	1-2 days	7-10
Acetyl-digitoxin	Acylanid (Sandoz)	2-4 hr	8-10	2 days	7-14
Digitoxin	Digitaline Nativelle Crystodigin (Lilly) Purodigin (Wyeth)	2-4 hr	12	2 days	10-14
Digitalis leaf	Digitalis U S P	3-6 hr	36	2 days	10-21

G) and *strophanthin K*. The available commercial preparations, their route of administration, onset, and duration of action are shown in Table 18-21.

Specific Characteristics of Various Digitalis Preparations

1. *Ouabain and strophanthin* are the most potent agents available. As seen in Table 18-21, following intravenous injection, they have extreme speed of action and onset of peak effect, and rapid rate of dissipation. This makes them ideally suited for emergency therapy. They are not absorbed when taken orally.

2. *Deslanoside* (*acetyl-lanatoside C or Cedilanid D*) is derived from lanatoside C. It is similar to digoxin in its action but may have a more rapid action and an earlier peak effect. *It is therefore suitable for emergency therapy and for rapid digitalization by either intravenous or intramuscular injection.* Its rapid dissipation makes it unsuitable for oral maintenance therapy.

3. *Digoxin* is suitable for both parenteral and oral digitalization and for long-term maintenance. It may be more difficult to establish a stable maintenance dose with digoxin than with other preparations because of its relatively rapid dissipation. However, *this makes it a desirable drug in situations where rapid withdrawal of digitalis is desirable or where digitalis toxicity is likely to occur* (*as in potassium depletion, elderly individuals, etc.*)

4. *Digitoxin*, one of the most widely used glycosides, is an excellent preparation for both intramuscular and oral use initially, and *is particularly suited for long-term oral maintenance* because of its constancy of absorption and relatively slow dissipation. It is also said to cause less gastrointestinal irritation. Because of this, however, one must guard against overdosage and cumulative effects.

5. *Digitalis leaf* has been largely replaced by the more purified glycosides during initial, oral digitalization, particularly when a rapid effect is desired. Its use is associated with a higher incidence of nausea and vomiting. However, it remains a satisfactory preparation for oral maintenance therapy because of its slow dissipation; here, too, one must guard against cumulative effects.

6. *Gitalin* lies between digoxin and digitoxin in its speed of action and peak effects and rate of dissipation. It has been claimed that its therapeutic range is greater than that of other glycosides, and that digitalization can be attained with a lower incidence of toxicity. It is a good drug for oral digitalization and for maintenance therapy, particularly in patients who have previously shown toxic effects from other preparations.

OTHER DIFFERENCES IN CLINICAL EFFECTS. Recent clinical studies (Aravanis *et al.*) have shown qualitative and quantitative differences among the various glycosides when administered parenterally, which can be applied to clinical situations:

2. The direct myocardial action increases the force of myocardial contractions by a mechanism not sufficiently understood.

3. Digitalis enhances the mechanical efficiency of the contractile units of the failing myocardium by restoring a more smooth transition from chemical energy (ATP, ADP) to mechanical energy of contraction. This makes the drug highly effective in clinical states associated with hypertrophy and dilatation of the cardiac fibers without too much damage but with low cardiac output. In such states, the diminished contractile response of the failing myocardium to an undiminished supply of chemical energy can be improved, and the cardiac output increased. The effect is inadequate in toxic and inflammatory disorders affecting the energy-supplying areas of the cardiac fiber (nucleus and mitochondria), as in diphtheritic or viral myocarditis.

4. Digitalis decreases the diastolic length of the failing cardiac fibers, diminishes their oxygen consumption for any given work output, and thereby increases the work capacity and efficiency of the failing heart.

5. Since digitalis does not affect the energy-producing mechanism of the cardiac fiber, it is of little value in heart failure associated with high cardiac output due to causes which affect the metabolic processes of the myocardium, such as thyrotoxicosis or beriberi

Digitalization, therefore, in conjunction with rest, constitutes the most effective direct measure for increasing the efficiency and output of the heart, in contradistinction to diuretics, which alleviate edema primarily by their effects on the kidney.

Clinical Indications. Digitalis is indicated in almost all types of heart failure, whether purely left-sided, right-sided, or combined, whether acute or chronic, and of all causes. It should be the initial treatment and should not be replaced by diuretics except in special circumstances It is effective in heart failure caused by congenital, rheumatic, hypertensive, or arteriosclerotic heart disease with cardiac dilatation, impaired myocardial contraction, and reduced cardiac output It is of particular value in heart failure associated with paroxysmal tachycardia or other arrhythmias with rapid ventricular rate resulting in inefficient atrial and ventricular contractions. It is of less value in acute inflammatory and toxic myocardial involvement, as in acute myocarditis (bacterial, viral, rheumatic) or acute necrosis of the myocardium (myocardial infarction), where the damage is extensive and results in lysis of the energy-forming parts of the myocardial cells. Even in these conditions, the drug may be of value if the myocardial involvement is not too widespread and if there are remaining viable but dilated cardiac fibers whose mechanical efficiency can be sufficiently improved to restore some degree of cardiac compensation As already stated, the drug is not too effective in metabolic and nutritional disorders resulting in failure (hyper- and hypothyroidism, beriberi and anoxic states, and pulmonary disorders resulting in cor pulmonale). Although *digitalis is not contraindicated in these conditions*, it must be kept in mind that, despite adequate digitalization, heart failure will not be controlled unless the underlying cause is adequately treated.

Pharmacologic Differences of Various Glycosides and Their Clinical Applications. Most digitalis preparations have basically the same action on the heart, but there are qualitative and quantitative differences which are related to differences in rate and degree of absorption and excretion, potency, onset of peak effect, and duration of action.[2] These differences determine the suitability of the various glycosides for oral and parenteral use, for rapid digitalization, and long-term maintenance therapy. The practicing physician would find it difficult to use every available preparation, but he should become familiar with the several oral and parenteral preparations for routine use and should be aware of the effects of all the other preparations and their availability for special situations

There are three main glycosides: digitoxin, gitoxin, and digoxin, which are derived from two digitalis plants, *Digitalis lanata* and *Digitalis purpurea* (Fig. 21-31) Of these, only *digitoxin* and *digoxin* and their derivatives have important cardiac effects Intermediate preparations of the digitoxin glycosides are *lanatoside A* and *acetyl-digitoxin;* of the digoxin glycoside, *lanatoside C, acetyl-digoxin*, and *desacetyl-lanatoside C* (*deslanoside, Cedilanid D*)

Gitalin is derived from *D. purpurea* and is a combination of glycosides (gitoxin, digitoxin, gitaloxin, strospeside). Digitalis (USP) is a dried extract of the whole leaf of *D. purpurea* containing variable amounts of the above glycosides.

The strophanthus plants yield two complexes of rapidly acting glycosides· ouabain (*strophanthin*

[2] See Part 21, Chap. 10. *Editor.*

patients and in those with mild to moderate degrees of failure

INITIAL DIGITALIZATION. *There is no fixed dosage for optimal digitalization and no mathematic method for determining dosage.* The dose necessary to achieve the desired therapeutic effect without producing toxicity must be reached carefully in each patient. The size of the initial dose and of subsequent doses, as well as the interval between doses, depends on the severity of the heart failure and the acuteness of the symptoms. Thus, digitalization can be achieved either rapidly or slowly, depending on the size and frequency of the dosage and the amount by which the total 24-hr dose exceeds the amount excreted or dissipated in the body. There may be wide variations in the required dosage from patient to patient

Rapid digitalization is achieved by giving a relatively large initial dose of the drug, either orally or parenterally, followed by a smaller dose at 6- to 12-hr intervals for 24 to 48 hr. The initial dose is generally one fourth to one-half of the average total digitalizing dose of each preparation (Table 18-22), and the subsequent doses generally range from one-sixth to one-fourth of the total dose With this method, a full therapeutic effect can be obtained within 48 hr The onset of clinical improvement is generally evident after about half the digitalizing dose has been given.

When digitalization has been started with a parenteral preparation (deslanoside, 0.8 mg intravenously), it can be continued by giving an oral preparation the same day.

According to Neumann and Reich, 0.4 mg digitoxin should be given orally on the same day as the intravenous injection, a similar dose should be given on the following day; then, 0.2 mg should be given on the third day, followed by a maintenance daily dose of 0.1 mg if a full therapeutic effect has been obtained. A slightly less effective scheme consists of 0.2 mg on the day of the injection, as well as on the second and third days.

Moderately rapid digitalization may be achieved by giving one-third of the minimal recommended therapeutic dose daily in two divided doses for 3 days For example, digitoxin 0.2 mg is given twice daily for 72 hr, for a total of 1.2 mg A therapeutic effect (decrease of dyspnea and edema, slowing of heart rate, etc.) should become evident by this time in most patients. One-half this dosage can be continued cautiously for several days if a full therapeutic effect has not been obtained, and then the usual daily maintenance dose of 0.1 mg is started

Slow digitalization, usually indicated in ambulatory patients with mild failure, is attained by giving a small fraction of the average total therapeutic dose (one-eighth to one-sixth), three times daily for 3 to 4 days, and by then reducing to twice daily until a good clinical

TABLE 18-22. AVERAGE THERAPEUTIC DOSE OF DIGITALIS PREPARATIONS (24 TO 48 HR)

Preparation	Parenteral			Oral			
	Initial	*Subsequent*	*Total*	*Initial*	*Subsequent (4–6 hr)*	*Total*	*Daily maintenance dose*
Ouabain, mg	0.5	0.25–0.5	0.5–1.0	Not used			
Deslanoside, mg	0.8	0.4–0.8 q 4 hr	1.6–2.0	Not used			
Lanatoside C, mg				3–5	0.75–1.0	7.5–10	0.75–1.0
Gitalin, mg	2.5	1.0 q 6 hr	4.0–5.0	1.5–2.5	0.75	5.5 (3.0–10)	0.5
Digoxin, mg	0.5–1.0	0.5 q 6–12 hr	2.0–2.25	1.0–1.5	0.25–0.5	2.5 (2.0–3.5)	0.25–0.5
Digitoxin, mg	0.6	0.2 q 6–12 hr	1.2–1.4	0.4–0.8	0.2–0.4	2.0 (1.2–3.0)	0.1–0.15
Acetyl-digitoxin, mg	0.8	0.2 q 6–12 hr	1.2–1.6	0.6–0.8	0.2–0.4	1.2–2.0	0.1–0.2
Digitalis leaf, Gm		Not used		0.4–0.8	0.2–0.4	1.6 (1–3.5)	0.1

1. Digoxin and deslanoside produced the greatest slowing of the heart rate, making them preferable in severe tachycardias and atrial arrhythmias.

2. Ouabain (first and second days) and digitoxin (second day) caused the fastest onset of improvement, as compared with digoxin and gitalin (third day) and acetyl-digitoxin (third to fourth days). This rapid effect of parenterally administered digitoxin has not been sufficiently appreciated.

3 Digitoxin, acetyl-digitoxin, and digoxin produced the best effect on cardiac dilatation (shown by radiography) and venous engorgement (shown by size of liver, venous pressure, and circulation times).

4. The greatest effects on the electrocardiogram (RS-T depression and T-wave inversion) were caused by digitoxin. Acetyl-digitoxin, deslanoside, and digoxin produced the greatest clinical improvement with least electrocardiographic change. This would suggest that when severe electrocardiographic changes are present because of myocardial damage and left ventricular strain, these preparations are preferable to digitoxin

5. The minimum toxic reactions were observed with deslanoside, followed by acetyl-digitoxin and digitoxin, making these, especially deslanoside, the preferred preparations in patients with low threshold of toxicity A relatively high incidence of toxicity occurred with digoxin, probably because the generally recommended dosage for parenteral administration has been too high (3 mg in 48 hr instead of 2 mg).

These pharmacologic differences in the various digitalis preparations would suggest the following clinical applications in the management of patients with heart failure:

1 In mild to moderate failure, especially in ambulatory patients, one should digitalize orally by slow or rapid method with digitalis leaf, digitoxin, acetyl-digitoxin, gitalin, or digoxin.

2. In severe failure and in situations of moderate urgency, one should digitalize rapidly and orally with digoxin, gitalin, digitoxin, or acetyl-digitoxin.

3. For emergency situations, such as acute pulmonary edema and severe tachycardia, one should digitalize rapidly and parenterally with ouabain, deslanoside, digoxin, or digitoxin.

Dosage and Methods of Administration. There are several cardinal principles of successful digitalis therapy.

1. The physician should be familiar with the characteristics of each available preparation, as already discussed and outlined in Tables 18-21 and 18-22.

2. The specific preparation should be given in adequate dosage to produce the optimum therapeutic effect.

3. Dosage should be carefully regulated to avoid risk of toxicity.

4. The type of preparation used and the route of administration depend on the urgency of the clinical situation and the severity of the heart failure.

Initial digitalization in a previously undigitalized or underdigitalized patient should be considered a clinical experiment; it is basically an attempt by trial and error to administer a therapeutically effective dose without producing toxic symptoms. Although the therapeutic dose for individual patients varies, there is generally an optimum therapeutic range for each digitalis preparation, below which the clinical response is inadequate, and above which toxicity will generally develop. After the desired therapeutic effect is obtained, the dosage is reduced to a maintenance dose calculated for each patient

ROUTE OF ADMINISTRATION. The parenteral administration of a digitalis preparation, either intravenously or intramuscularly, is indicated only in acute emergencies, such as pulmonary edema and acute heart failure associated with serious cardiac arrhythmias or excessive tachycardia It also may be indicated in patients with nausea and vomiting who cannot take oral medication. Ouabain, strophanthin, deslanoside, digoxin, and digitoxin can be given parenterally The first two must be given intravenously, the last three may be given intravenously or intramuscularly. In patients in shock or with severe tissue edema, absorption following intramuscular injection may be irregular and local tissue irritation and occasional necrosis may occur. The oral route is suitable for the great majority of patients with failure. Peak effects can be obtained within several hours, and excellent therapeutic results may be achieved within 1 to 3 days with any of the available oral preparations mentioned previously. It is the preferable route for ambulatory

patients and in those with mild to moderate degrees of failure.

INITIAL DIGITALIZATION *There is no fixed dosage for optimal digitalization and no mathematic method for determining dosage.* The dose necessary to achieve the desired therapeutic effect without producing toxicity must be reached carefully in each patient. The size of the initial dose and of subsequent doses, as well as the interval between doses, depends on the severity of the heart failure and the acuteness of the symptoms. Thus, digitalization can be achieved either rapidly or slowly, depending on the size and frequency of the dosage and the amount by which the total 24-hr dose exceeds the amount excreted or dissipated in the body. There may be wide variations in the required dosage from patient to patient.

Rapid digitalization is achieved by giving a relatively large initial dose of the drug, either orally or parenterally, followed by a smaller dose at 6- to 12-hr intervals for 24 to 48 hr. The initial dose is generally one-fourth to one-half of the average total digitalizing dose of each preparation (Table 18-22), and the subsequent doses generally range from one-sixth to one-fourth of the total dose. With this method, a full therapeutic effect can be obtained within 48 hr. The onset of clinical improvement is generally evident after about half the digitalizing dose has been given.

When digitalization has been started with a parenteral preparation (deslanoside, 0.8 mg intravenously), it can be continued by giving an oral preparation the same day.

According to Neumann and Reich, 0.4 mg digitoxin should be given orally on the same day as the intravenous injection; a similar dose should be given on the following day; then, 0.2 mg should be given on the third day, followed by a maintenance daily dose of 0.1 mg if a full therapeutic effect has been obtained. A slightly less effective scheme consists of 0.2 mg on the day of the injection, as well as on the second and third days.

Moderately rapid digitalization may be achieved by giving one-third of the minimal recommended therapeutic dose daily in two divided doses for 3 days. For example, digitoxin 0.2 mg is given twice daily for 72 hr, for a total of 1.2 mg. A therapeutic effect (decrease of dyspnea and edema, slowing of heart rate, etc.) should become evident by this time in most patients. One-half this dosage can be continued cautiously for several days if a full therapeutic effect has not been obtained, and then the usual daily maintenance dose of 0.1 mg is started.

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Lanatoside C, mg				3–5	0.75–1.0	7.5–10	0.75–1.0
Gitalin, mg	2.5	1.0 q 6 hr	4.0–5.0	1.5–2.5	0.75	5.5 (3.0–10)	0.5
Digoxin, mg	0.5–1.0	0.5 q 6–12 hr	2.0–2.25	1.0–1.5	0.25–0.5	2.5 (2.0–3.5)	0.25–0.5
Digitoxin, mg	0.6	0.2 q 6–12 hr	1.2–1.4	0.4–0.8	0.2–0.4	2.0 (1.2–3.0)	0.1–0.15
Acetyl-digitoxin, mg	0.8	0.2 q 6–12 hr	1.2–1.6	0.6–0.8	0.2–0.4	1.2–2.0	0.1–0.2
Digitalis leaf, Gm	Not used			0.4–0.8	0.2–0.4	1.6 (1–3.5)	0.1

1. Digoxin and deslanoside produced the greatest slowing of the heart rate, making them preferable in severe tachycardias and atrial arrhythmias.

2. Ouabain (first and second days) and digitoxin (second day) caused the fastest onset of improvement, as compared with digoxin and gitalin (third day) and acetyl-digitoxin (third to fourth days). This rapid effect of parenterally administered digitoxin has not been sufficiently appreciated.

3. Digitoxin, acetyl-digitoxin, and digoxin produced the best effect on cardiac dilatation (shown by radiography) and venous engorgement (shown by size of liver, venous pressure, and circulation times).

4. The greatest effects on the electrocardiogram (RS-T depression and T-wave inversion) were caused by digitoxin. Acetyl-digitoxin, deslanoside, and digoxin produced the greatest clinical improvement with least electrocardiographic change. This would suggest that when severe electrocardiographic changes are present because of myocardial damage and left ventricular strain, these preparations are preferable to digitoxin

5. The minimum toxic reactions were observed with deslanoside, followed by acetyl-digitoxin and digitoxin, making these, especially deslanoside, the preferred preparations in patients with low threshold of toxicity. A relatively high incidence of toxicity occurred with digoxin, probably because the generally recommended dosage for parenteral administration has been too high (3 mg in 48 hr instead of 2 mg).

These pharmacologic differences in the various digitalis preparations would suggest the following clinical applications in the management of patients with heart failure.

1. In mild to moderate failure, especially in ambulatory patients, one should digitalize orally by slow or rapid method with digitalis leaf, digitoxin, acetyl-digitoxin, gitalin, or digoxin.

2. In severe failure and in situations of moderate urgency, one should digitalize rapidly and orally with digoxin, gitalin, digitoxin, or acetyl-digitoxin.

3. For emergency situations, such as acute pulmonary edema and severe tachycardia, one should digitalize rapidly and parenterally with *ouabain, deslanoside,* digoxin, or digitoxin.

Dosage and Methods of Administration. There are several cardinal principles of successful digitalis therapy.

1. The physician should be familiar with the characteristics of each available preparation, as already discussed and outlined in Tables 18-21 and 18-22.

2. The specific preparation should be given in adequate dosage to produce the optimum therapeutic effect.

3. Dosage should be carefully regulated to avoid risk of toxicity.

4. The type of preparation used and the route of administration depend on the urgency of the clinical situation and the severity of the heart failure.

Initial digitalization in a previously undigitalized or underdigitalized patient should be considered a clinical experiment; it is basically an attempt by trial and error to administer a therapeutically effective dose without producing toxic symptoms. Although the therapeutic dose for individual patients varies, there is generally an optimum therapeutic range for each digitalis preparation, below which the clinical response is inadequate, and above which toxicity will generally develop. After the desired therapeutic effect is obtained, the dosage is reduced to a maintenance dose calculated for each patient.

ROUTE OF ADMINISTRATION. The parenteral administration of a digitalis preparation, either intravenously or intramuscularly, is indicated only in acute emergencies, such as pulmonary edema and acute heart failure associated with serious cardiac arrhythmias or excessive tachycardia It also may be indicated in patients with nausea and vomiting who cannot take oral medication. Ouabain, strophanthin, deslanoside, digoxin, and digitoxin can be given parenterally. The first two must be given intravenously, the last three may be given intravenously or intramuscularly. In patients in shock or with severe tissue edema, absorption following intramuscular injection may be irregular and local tissue irritation and occasional necrosis may occur. The oral route is suitable for the great majority of patients with failure. Peak effects can be obtained within several hours, and excellent therapeutic results may be achieved within 1 to 3 days with any of the available oral preparations mentioned previously. It is the preferable route for ambulatory

advanced cardiac disease with failure, the myocardium may become unresponsive to the usually recommended maintenance dose and toxicity may occur before a therapeutic effect. In such patients, the maintenance dose will be the largest dose the patient can tolerate without causing toxic effects.

Average Predicted Dose for Each Preparation. Comparative studies on ambulatory patients have indicated the following comparable *maintenance doses* (Table 18-23) to be adequate in about 75 per cent of patients. Generally, with slowly excreted glycosides (digitoxin), the maintenance dose is about one-tenth the digitalizing dose. With more rapidly excreted glycosides (digoxin) this fraction increases to about one-sixth to one-eighth. If an inadequate response is observed with this dose, then it should be increased by 50 per cent or doubled until the desired effect is obtained Also, it may be helpful to switch from one preparation to another, and determine by trial and error whether one is preferable to the other. It can be seen in Table 18-23 that *the usual maintenance dose of the leaf* (0 1 Gm) *is equivalent to 0 1 mg digitoxin, 0 5 mg digoxin, 0 5 mg gitalin, and 1 0 mg deslanoside.* Although these dosages will be therapeutically effective in about 75 per cent of patients, a smaller group (15 per cent) may require a larger dose, and a small percentage (10 per cent) may show toxic signs with the recommended dosage In about 10 per cent of patients, no therapeutic effect can be maintained with any of the digitalis preparations

GUIDES TO DETERMINING MAINTENANCE DOSAGE

Control of Congestive Signs As in initial digitalization, the best guide to determining adequate maintenance dosage is the effect on edema and other signs of failure. If signs of early failure recur (ankle edema, increased weight), the maintenance dose should be doubled for several days. Such intermittent increase in dosage may be necessary frequently. With few exceptions, patients with class II or III heart disease who have been digitalized during bouts of acute heart failure should continue the digitalis maintenance therapy indefinitely. Stopping the drug for more than a few days may result in recurrence of edema, dyspnea, or other signs of failure unless the patients are receiving other potent diuretics. However, if the patient is completely free of signs of failure, skipping the dose for 1 or 2 days each week, particularly if digitoxin or whole leaf is used, may be adequate for maintenance and help to prevent toxicity. Also, the daily maintenance dose can be reduced, for example, digoxin 0.25 mg rather than 0 5 mg.

Heart Rate When atrial fibrillation is present, the ventricular response should not be allowed to slow below 50 beats per minute and preferably should not be more than 80 beats per minute at rest When normal sinus rhythm is present, the heart rate is not a good guide to maintenance dosage, except that either marked tachycardia or bradycardia may be a sign of digitalis toxicity. Ordinarily, however, there is no indication for discontinuing or skipping the daily dose when the rate falls to 60 beats per minute or even less.

Electrocardiogram. The severity of the electrocardiographic changes produced by digitalis is no effective guide to the degree of digitalization necessary for maintaining dosage: RS-T and T-wave changes may occur even when the dosage is inadequate, and toxicity may be

TABLE 18-23 MAINTENANCE DOSAGE OF DIGITALIS PREPARATIONS

Drug	*Average daily maintenance dose*	*Range*	*Ease of maintenance*	*Dissipation*	*Duration of toxic effects*
Deslanoside, mg	1 0	0 75–1 25			
Digoxin, mg	0 5	0 25–0 75			
Gitalin, mg	0 5	0 5–0 75			days)
Digitoxin, mg	0 1	0.075–0 125			[illegible] days)
Acetyl-digitoxin, mg	0 1	0 1–0 2	Good	Moderate (2 wk)	Short (1–3 days)
Digitalis leaf, Gm	0 1	0 05–0 15	Good	Slow (2 wk)	Prolonged (3–10 days)

effect is observed, generally within 1 week, or until toxic signs appear. A similar result can be attained by giving a single daily dose, generally equal to one and one-half to two times the average maintenance dose, for 1 week, and then starting the daily maintenance dose.

Guides to Optimal Therapeutic Dosage. The average range of the therapeutic and toxic doses for several commonly used digitalis preparations is given in Table 18-22, for both initial digitalization and maintenance. These average dosages have been determined empirically by clinical observation in large groups of patients (Batterman, Luisada). A good and prompt clinical effect can be attained in most cases by adhering to these recommended dosage schedules. However, the optimal dose for each individual must be determined by the effects on the clinical manifestations of the heart failure. Except in severe heart failure, it is not necessary or practical to try to attain maximal dosage. In such cases, the dosage may be cautiously increased above the recommended therapeutic dose until the desired improvement is observed or until signs of digitalis toxicity begin to appear. Then the dose is reduced to the recommended average maintenance dose.

The following criteria may serve as useful guides in determining when the digitalizing dose is adequate:

SLOWING OF HEART RATE. In the presence of atrial fibrillation, the ventricular rate is a sensitive index of the level of digitalization. Slowing of the apical rate to 60 to 70 per minute at rest and disappearance of a pulse deficit are the desired effects. After exercise or excitement, the apical rate should not increase more than 10 to 20 beats per minute. In the presence of normal sinus rhythm, however, the effect on heart rate is much less striking, but here, too, slowing of the rate is an excellent indication of improved myocardial function. Since clinical improvement may appear before there is significant slowing of the heart rate, the latter should not be used as the only guide to dosage. Unlike the case of atrial fibrillation, where the slowing of the ventricular rate may be due largely to vagal stimulation and depression of AV conduction, the slowing of sinus tachycardia is chiefly due to the myocardial effects of digitalization (increased stroke output). In the presence of fever, infection, or hyperthyroidism, one should not expect to reduce the heart rate to normal levels. Attempts to do so would result in digitalis toxicity.

DIURETIC EFFECT. This is the most important indication of a good therapeutic effect. A good diuresis with progressive weight loss and disappearance of edema and other congestive signs indicates restoration of myocardial efficiency, increased cardiac output, and reversal of the hemodynamic disturbances in the kidney.

DISAPPEARANCE OF VENOUS CONGESTION. Disappearance of dyspnea and orthopnea, edema, and enlarged liver are excellent guides to a good clinical effect. These signs result from the improved myocardial function, diuresis, and direct effect on venous circulation. Observation of the venous pressure and circulation time provides a simple objective confirmation of this result.

CARDIAC SIZE. Decrease of diastolic heart size, shown by serial roentgenograms, indicates decreasing cardiac dilatation and is one of the important therapeutic effects of full digitalization.

Maintenance Therapy. The maintenance dose of any digitalis preparation is that amount required to maintain the improved myocardial efficiency produced by initial digitalization. *It varies with the rate of dissipation, cumulative action, and therapeutic range of each preparation, and with the cardiac reserve of the patient.* Regulation of the maintenance dose is of great importance. An inadequate dosage may allow the therapeutic effect to be dissipated, and the failure to recur; too large a dose may cause digitalis toxicity. Similarly, skipping the dose, even for a few days, may bring the patient's digitalis concentration below the therapeutic level, and signs of failure may recur.

DETERMINATION OF MAINTENANCE DOSE. Like calculation of the therapeutic dose for initial digitalization, determination of the daily maintenance dose is also a matter of trial and error. With each digitalis preparation, it depends on several factors.

The Amount of Drug Necessary to Achieve Full Digitalization. It is evident that a patient who required 4.0 mg digoxin initially will require a larger maintenance dose (probably 0.5 mg) than one who required at first only 2.5 mg (probably 0.25 mg).

The Severity of the Underlying Cardiac Disease. Patients with hypertrophied hearts generally require a larger maintenance dose. However, with increasing cardiac damage and in

by vomiting, salivation, and occasionally diarrhea. These symptoms may occur with either oral or parenteral medication and are central in origin. They occur several hours after administration of a large dose or during prolonged maintenance therapy, and are generally persistent. They must be distinguished from the occasional local gastrointestinal irritation, which is generally a temporary side effect, and from the nausea and vomiting of right heart failure produced by engorgement of the gastrointestinal tract and liver, which improves with therapy. Gastrointestinal irritation is more frequent with whole digitalis leaf, because of the presence of gitoxin, and less frequent with the pure glycosides.

Neurologic Symptoms and Signs. These are caused by visual and cerebral irritation and depression, and are manifested by headache, mental depression, confusion or delirium (especially in elderly patients), vertigo, yellow vision and other disturbances in color vision, and retrobulbar neuritis producing scotomas and transient blindness.

Cardiac Manifestations. These are produced by (1) increased irritability of the atrial and ventricular myocardium and of the SA and AV nodal pacemakers, causing various types of arrhythmia and tachycardia, (2) depression of the SA and AV nodal pacemakers and of the AV conduction system, causing a variety of conduction disturbances, and (3) disturbance of cardiac contractility due to degeneration and necrosis of the myocardium.

1. *Myocardial irritability* may produce numerous *ectopic rhythms*, particularly atrial or ventricular premature beats, atrial or ventricular tachycardia, and AV *dissociation* (double tachycardia). *Ventricular extrasystoles* and *bigeminal rhythm* are often the earliest signs of toxicity and may progress to multifocal ectopic beats and unidirectional or bidirectional ventricular tachycardia. *Atrial tachycardia with block* is a characteristic manifestation of digitalis toxicity but is not specific for it, occurring occasionally in undigitalized patients. Other atrial arrhythmias, such as *atrial flutter* and *atrial fibrillation*, may occur but are less common. Intensification of sinus tachycardia may also be a toxic sign.

2. *Disturbances of conduction*, including sinus bradycardias, SA *block*, nodal bradycardia, and wandering pacemaker, may occur because of the direct depressant effect of the drug on the SA and AV pacemakers and because of vagal stimulation. Impaired AV conduction may result in all degrees of *AV block*, from prolongation of the P-R interval to partial block with dropped beats and Wenckebach periods, to complete AV block. Regularization of ventricular rhythm in long-standing atrial fibrillation may be due to AV block rather than reversion to normal rhythm.

3. *Myocardial degeneration and necrosis* produced by digitalis overdosage may result in increasing severity of heart failure, often following an initial improvement. In such cases the failure may decrease when the digitalis is discontinued.

DIAGNOSIS OF DIGITALIS TOXICITY AND ITS PREVENTION

1. *The sudden appearance of any cardiac arrhythmia* in a patient receiving digitalis should be suspected to be a sign of digitalis toxicity. This may occur with large oral doses or intravenous therapy, especially when the patient has previously received digitalis. Serious cardiac arrhythmias may occur in the absence of gastrointestinal or neurologic symptoms.

2. *Loss of appetite and anorexia* are the most common symptoms of toxicity during maintenance therapy. The patient must be alerted to their significance so that the drug can be stopped promptly.

3. *Periodic check of serum electrolytes* is important when the patient is receiving combined digitalis and diuretic therapy. *Acidosis* and *hypopotassemia* may predispose to myocardial irritability and ectopic rhythms. To prevent hypopotassemia, the diuretic agent should be supplemented with potassium salts, such as potassium chloride, 0.5 Gm t.i.d., or potassium Triplex (a combination of potassium chloride, nitrate, and citrate), 5 ml t.i.d.

4. *Calcium salts* should be given with caution to digitalized patients because of their synergistic action. Also, large amounts of oral or parenteral carbohydrates should be avoided, as well as hyperinsulinism.

5. *Acetyl-strophanthidin Test for Digitalis Toxicity:* When digitalis toxicity is suspected, it is generally safe to discontinue the drug temporarily to observe whether the symptoms or cardiac signs disappear. In severe failure, however, it may be difficult to determine if the patient is under- or overdigitalized. Stopping the drug may lead to increasing failure if the patient is underdigitalized, and continuing the

reached without significant electrocardiographic changes. A slightly prolonged P-R interval also has no significance. However, cardiac arrhythmias and a more advanced degree of AV block indicate digitalis toxicity and are indications for temporarily discontinuing and then lowering the maintenance dose.

DURATION OF MAINTENANCE THERAPY. As stated above, when a dilated, damaged heart has failed, and compensation has been restored with digitalis and other diuretic therapy, it is generally advisable to continue maintenance digitalization indefinitely, in an attempt to prevent recurrent bouts of failure. This applies to heart failure produced by arteriosclerotic, hypertensive, and valvular heart disease. However, not infrequently heart failure may occur in a patient with mild heart disease under the influence of severe overloading of the circulation. In such a patient, the cardiac reserve is restored to normal when the precipitating factor is eliminated and heart failure would not be expected to recur except under unusual circumstances.

Examples of this situation are surgical and postoperative stresses, pregnancy, severe pneumonia, etc. In such cases, digitalis maintenance may be cautiously discontinued several months later if cardiac function appears normal. Similarly, a patient with heart failure due to acute myocardial infarction or acute myocarditis may recover completely and subsequently may show no cardiac enlargement and normal cardiac reserve. Such a patient may remain free of failure when digitalis is discontinued, provided other measures are followed to avoid overloading of the heart and circulation, such as avoidance of excessive exertion, low salt intake, intermittent diuretic therapy, etc. Before and after discontinuing or lowering the dose of digitalis, the patient's response to increased activities should be carefully observed, since his digitalis requirement is greater when he is active than when he is at rest, and the signs of recurrent failure may be delayed for several weeks after the digitalis effect is completely dissipated.

Digitalis Toxicity. With the wide use of highly purified and potent glycosides and the introduction of more potent oral diuretics, the problem of digitalis toxicity remains serious. It is related to several factors.

1. The range between the effective therapeutic level and the toxic level of all digitalis preparations is relatively small. In many cases, the toxic dose may be reached before a good clinical response is obtained, particularly in advanced heart disease. For this reason, it is again emphasized that active digitalization should not be carried out by a fixed dosage schedule, and that the clinical status and the electrocardiogram should be checked carefully before each dose change.

2. There is a wide variation in the dose of any digitalis preparation required to produce a good therapeutic response or a toxic effect. Although the average predicted digitalizing dose may be effective and safe in approximately two-thirds of patients, a small group may require up to double this amount to achieve a clinical effect and other patients may develop toxic signs before the therapeutic dose has been reached.

3. Elderly patients, generally those over 60 years of age, may require less digitalis for a therapeutic effect because of slower dissipation and excretion. Also, a sensitive carotid sinus may be activated by the vagal effects of digitalis, producing undesirable effects on the heart rate and rhythm.

4. Patients with severe right heart failure may excrete digitalis slowly, particularly in the first 24 hr.

5. Electrolyte disturbances (especially potassium depletion) produced by concurrent mercurial or thiazide diuresis predispose to digitalis toxicity.

6. Digitalis preparations vary in their rate of dissipation, duration of action, and cumulative effect, so that toxicity may develop more easily with slowly dissipated preparations (digitoxin, digitalis leaf) than with rapidly excreted preparations (digoxin, gitalin). Similarly, the duration of toxic signs, when they develop, varies with the rate of dissipation of the drug. On the other hand, a purified glycoside such as digitoxin, with constancy of absorption and excretion, should cause fewer toxic reactions if the dose is carefully regulated. In the past, toxic reactions with digitoxin often were attributable to the recommended maintenance dose (0.2 mg), which was too large for most patients.

SYMPTOMS AND SIGNS OF DIGITALIS TOXICITY. Allergic reactions and idiosyncrasy to digitalis may occur but are rare. They are manifested by skin eruptions, gastrointestinal disturbances, and eosinophilia. In most cases, reactions are due to toxic effects from overdosage.

Gastrointestinal Symptoms. Loss of appetite and nausea are the early symptoms, followed

renal tubular function is unimpaired in congestive failure, except in terminal failure and in severe ischemic states, where tubular necrosis may occur. Diuretic agents counteract or block the physiologic functions of the proximal and distal tubules involved in the active reabsorption and conservation of sodium and chloride and the passive reabsorption of water, which are enhanced in congestive heart failure

In addition to their primary renal effect, diuretic agents may also favorably influence myocardial function by increasing the cardiac output and reducing venous, atrial, and ventricular diastolic pressures. With the exception of the *xanthines*, however, this results from the increased diuresis of salt and water rather than from a direct effect on cardiac output or renal blood flow The increased diuresis reduces the extracellular and total blood volumes and leads to redistribution of blood from the engorged veins and capillary spaces, thereby increasing the cardiac output The elimination of edema in the lungs, pleural spaces, liver, and peripheral tissues leads to decreased dyspnea, improved ventilatory and hepatic functions, and progressive weight reduction

Types of Diuretics. There are at least six major types of synthetic organic compounds, with different pharmacologic actions, that have wide clinical application as diuretic agents at present. Their intelligent use, alone, alternately or combined, and supplemented with rest, dietary sodium regulation, and digitalization, will result in successful management of most patients with heart failure. They are (1) organomercurials (block proximal tubular reabsorption of sodium), (2) xanthines (increase renal blood flow), (3) pyrimidines, thiouracils (block tubular reabsorption), (4) triazines (block tubular reabsorption of sodium and water), (5) sulfonamides. (*a*) carbonic anhydrase inhibitors (block hydrogen-sodium exchange in distal tubules), (*b*) thiazide derivatives (block proximal and distal tubular reabsorption of sodium and chloride), (6) synthetic steroids, spirolactones (aldosterone inhibitors).

Organomercurials. The organic mercurial compounds, the most widely used diuretic agents, are the most potent and safest for parenteral use They consist of approximately 40 mg Hg per 1 ml solution, combined either with 30 to 50 mg theophylline compound or sodium thioglycollate per milliliter The latter substances act as a carrier of the mercury ions, increase their solubility, stabilize the solutions, increase local absorption, and reduce local irritation After intramuscular or subcutaneous administration, absorption is generally complete in 1 hr Approximately 30 to 40 per cent of the mercury is excreted within 3 hr and 85 to 90 per cent within 24 hr. The prompt liberation of the mercury ion within the renal cortex accounts for the diuretic activity, for the excretion rates of mercury and sodium ions parallel each other. The mercury ions block the enzyme transport systems for reabsorption of sodium and chloride in the proximal renal tubules, producing a hypotonic urine with increase of free water as well as of sodium and chloride Recent studies suggest that reabsorption of sodium and water in the distal tubules is also blocked by mercury. Potassium excretion is slightly but not significantly increased and may be decreased by suppression of tubular secretion of potassium, minimizing the danger of potassium depletion. The diuretic effect is dependent on the availability of chloride and water, and is diminished in hypochloremia.

The prompt excretion of most of the mercury ion within 24 hr permits frequent injections if renal function is normal, even daily ones when indicated When absorption of the mercurial is delayed by severe heart failure or massive local edema, the diuretic response is decreased. Also, in the presence of renal insufficiency, the decreased rate of excretion may lead to mercury retention in the kidneys and, if repeated injections are given, toxic damage of the tubules may occur Severe electrolyte disturbances (hypopotassemia and hyponatremia) do not occur except in patients with advanced heart disease requiring very frequent injections of large doses. There are several good commercial preparations available: meralluride (Mercuhydrin), mercurophylline (Mercuzanthin), mersalyl (Salyrgan Theophylline), mercumatilin (Cumertilin), mercaptomerin (Thiomerin), and merethoxylline procaine (Dicurin). All six preparations are approximately equal in clinical effectiveness and are well absorbed. Mercaptomerin and Dicurin procaine are claimed to have the added advantage of lower toxicity and less irritation when given subcutaneously, but the former is about two-thirds as potent as meralluride.

INDICATIONS AND METHODS OF ADMINISTRATION. Despite the availability of the oral thiazide derivates, the mercurials have retained their importance in the treatment of acute heart failure, in acute emergencies (such as pulmonary edema), and in severe chronic edema These two classes of diuretics (mercurials and thiazides) are not mutually exclusive.

drug may lead to *serious toxicity* if he is overdigitalized. The acetyl-strophanthidin test may be of help in such a case.

Under continuous electrocardiographic monitoring, the patient is given a small intravenous dose (0.1 mg) of this rapidly acting glycoside every 5 to 10 min for a total dose of 0.5 mg. The drug is discontinued if any signs of increased myocardial irritability (premature beats) or conduction disturbance appears. If digitalis toxicity is present, these signs will appear in a few minutes. The test has been of value but may be dangerous and should be applied with caution. A potassium solution should be available for intravenous use in case of severe arrhythmia following the test.

TREATMENT OF DIGITALIS TOXICITY

1. The drug must be stopped immediately until all signs of toxicity have disappeared. This interval may range from 3 to 15 days, depending on the type and dosage of the preparation given.

2. If possible, any potent oral diuretics should also be discontinued; their use may have predisposed to the digitalis toxicity. In severe heart failure, where it would be undesirable to stop the diuretics, one should resort to agents that have less potassium-depleting action, such as mercurials, and should supplement the diuretic therapy with large doses of potassium salts (5 Gm potassium chloride in divided doses on day of and day after the injection).

3. When there is severe nausea and vomiting, the use of bismuth subcarbonate (30 mg) or cocaine (30 mg) by mouth may be of help as local sedatives. If the patient is dehydrated from vomiting and diarrhea, parenteral infusion of glucose and fluids is indicated.

4. *The potassium salts* are valuable agents in all cases of digitalis toxicity associated with myocardial irritability. Potassium salts decrease the myocardial effects of digitalis and are particularly valuable in the early stages of digitalis toxicity. If the patient is not nauseated, large oral doses should be given (5 to 7.5 Gm daily in divided doses). Giving the salt in chilled fruit juice may diminish gastric irritation. In nausea and vomiting, or severe toxicity, or in *acute emergencies*, such as severe paroxysmal tachycardia, intravenous administration is necessary, using a solution of 5.0 Gm potassium chloride per liter of 5 per cent glucose in water. The infusion is given at a fairly rapid rate (4 ml/min) until the arrhythmia stops. Generally, 300 to 500 ml solution (40 mEq of potassium chloride) is necessary for a therapeutic effect. Potassium therapy should be given with caution in the presence of renal insufficiency.

5. Arrhythmias not responding to potassium therapy should be treated with *procaine amide* orally if possible (1.0 Gm initially and 0.5 Gm every 4 to 6 hr) or parenterally (1.0 Gm intramuscularly or by slow intravenous infusion giving 50 to 100 mg every 2 min).

6. In the presence of SA and AV conduction disturbances, the use of potassium salts and procaine amide may be harmful because of their myocardial depressant effects. In such cases, repeated doses of *atropine sulfate* (0.6 mg orally or parenterally) and of *isoproterenol* (5 to 10 mg sublingually or 0.1 to 0.2 mg intramuscularly) may be beneficial.

7. *Chelating agents* may be of value by lowering the blood calcium, which accentuates the effects of digitalis. This treatment has been used to abolish serious cardiac arrhythmia, particularly frequent ectopic beats and atrial and ventricular tachycardia. Dramatic effects may occur following a rapid intravenous infusion of *sodium versenate* (Na EDTA), using a solution of 3 Gm in 300 ml fluid. Although the effects may be transient, this therapy may be useful in emergencies.

DIURETIC THERAPY

The introduction of new potent oral diuretics in the past decade has advanced the clinical importance and effectiveness of diuretic therapy for heart failure.[a] Such diuretics exert their primary action not on the impaired myocardial function but on the renal system, and reverse the process which led to excessive retention of sodium and water responsible for the edema.

The renal adjustments to the decreased cardiac output and reduced renal blood flow in congestive failure include a *decreased glomerular filtration rate*, which is the primary disturbance, and an *increased tubular reabsorption* of sodium and water, which is secondary. The tubular retention of sodium and water is the most powerful process; it is enhanced by hypothalamic reflexes resulting in increased secretion of antidiuretic hormone and by increased blood content of *aldosterone* (partly as a result of decreased inactivation in the congested liver). Recent studies have indicated that

[a] See Part 21, Chap. 9. *Editor.*

is to enhance diuresis by elevating serum chloride levels to 100 mEq/liter or more and urinary chlorides to 40 mEq/liter or more

Ammonium chloride is an effective agent for increasing the level of serum and urine chloride ions The chloride is substituted for carbonic acid in the kidneys, sodium is excreted with the chloride and carbonic acid is retained. The intracellular acidosis and acid urine (pH 5) are temporary, however, and are overcome by increased ammonia production in the kidney, so that in a few days the diuretic effect is gone Large doses are required, ranging from 6 to 10 Gm daily in divided doses (containing 120 to 200 mEq chloride) Although ammonium chloride is tolerated by most patients, gastric irritation (anorexia and nausea) often develops Enteric-coated tablets (1 Gm) may reduce gastric irritation but occasionally are not well absorbed. The drug is used intermittently for 3 or 4 days prior to a mercurial injection and then discontinued temporarily to avoid severe acidosis

Calcium chloride is not well tolerated orally, either, and produces gastric irritation in the required dosage It can be given intravenously in hypochloremia, in doses of 10 ml of the 25 per cent solution several times daily

The organic chlorides, *L-lysine and L-arginine monohydrochloride*, recently have received extensive trial and have been found to be more palatable and better absorbed, producing only occasional diarrhea and abdominal cramps There is less danger of liver toxicity with these agents than with ammonium salts Large doses (20 to 40 Gm daily) are required to deliver an adequate amount of chloride to the serum and kidneys These chlorides are given in four divided doses with cold fruit juices or milk A dose of 40 Gm contains approximately 200 mEq chloride, which in most cases is sufficient to produce adequate chloruresis, with a rise in the urinary chloride level to 40 mEq or more when given for several days prior to a mercurial injection In chronic cardiac edema resistant to mercurial therapy, a daily intravenous infusion of L-arginine monohydrochloride (42 Gm/500 ml) for 1 to 3 days, then combined with a daily mercurial injection for 3 days, has been reported to be more successful than oral therapy in producing hyperchloremia and restoration of responsiveness to the mercurial

Potassium chloride administration, in addition to providing chloride ions, may correct potassium deficiency, which is another cause of decreased response to mercurials Correction of hypopotassemic alkalosis resulting from previous excessive diuresis or severe heart failure is necessary to restore responsiveness to diuretics and decrease the danger of digitalis toxicity

Acetazolamide, alone or in combination with ammonium chloride, can also produce hyperchloremic acidosis and potentiate mercurial diuresis. It is given in doses of 500 mg daily for several days and discontinued 24 hr before the mercurial injection so as to avoid an antagonistic effect.

ORAL ORGANOMERCURIALS Prior to the availability of the thiazide agents, the most potent oral diuretics were the organomercurials, chlormerodrin (Neohydrin), and mercumatilin (Cumertilin). They were widely used for long-term maintenance therapy after the acute heart failure had been controlled with parenteral mercurials and digitalis. Clinical experience up to 1957 (Evans) indicated that the condition of many patients could be controlled with the oral preparations as well as with frequent injections of meralluride

The effective dose ranges between two and six tablets daily in divided doses, and in severe cases up to eight tablets Each tablet, containing 18 mg of the organomercurial, is equivalent to approximately 10 mg organic mercury, so that the average daily effective dose contains 40 to 48 mg Hg. However, only 5 to 10 per cent of the ingested mercury is absorbed and excreted, causing uncertain diuretic effects in some cases Unlike the effect of the carbonic anhydrase inhibitors and the thiouracils, the diuresis is continuous even on long-term administration

Strict attention must be paid to possible side effects and signs of mercurialism, which may occur not infrequently. These include metallic taste, nausea, abdominal cramps, gingivitis, and colitis Patients with signs of cardiac decompensation apparently tolerate the drug better than those who are edema-free Side effects are rare on a dose of three tablets daily or less Occasionally, even reducing the dose below this level does not eliminate gastrointestinal intolerance The other toxic effects and contraindications are the same as those listed for the parenteral mercurials.

The oral organomercurials represent a safe and effective method for maintaining continuous and uniform diuresis (Griffith) Although their use has been largely supplanted by the newer oral thiazide derivatives, they should not be discarded, for they still have an important place in long-term maintenance therapy in selected patients Since their pharmacologic action is mediated through different enzyme systems and their electrolyte excretion patterns differ, the use of these preparations alternately or in combination may be more effective than either one used alone When excessive potas-

Their combined or alternate use is necessary for successful therapy in most cases of severe edema.

The following applications of parenteral mercurial therapy are of value:

1. In *acute heart failure* of moderate to severe intensity, mercurial diuretic therapy should be instituted simultaneously with other measures, such as rest, diet, digitalization, oxygen therapy, etc. An intramuscular injection of 1.5 to 2.0 ml is given at once and may be repeated the next day. Subsequent doses are given every 2 to 4 days, depending on the severity and duration of the congestive symptoms and the diuretic response to each injection. Not more than 2 ml should be given in one dose; some patients respond well to only 1.0 or 1.5 ml. The intervals between injections should be *timed to allow complete excretion of the mercury* and to avoid excessive electrolyte depletion. The weight loss is a good indication of the diuretic response and should serve as a guide to frequency of repeated injections. A 24-hr weight loss of over 5 lb is undesirable. When a "relatively dry" weight is achieved (when the weight curve shows a plateau), the frequency of injection is diminished or the drug may be supplanted by an oral diuretic. Periodic determinations of serum electrolytes are useful to detect excessive depletion when frequent *injections are given*.

2. In *chronic congestive heart failure* with recurrent edema and serous effusions, mercurial injections are usually required regularly. Although such maintenance therapy has been partially, or in some cases completely, supplanted by the newer oral chlorothiazide derivatives, many patients cannot be maintained edema-free or in a comfortable state without additional parenteral therapy. In conjunction with oral therapy, 1- to 2-ml doses can be injected at intervals ranging from twice weekly to *every 2 to 4 weeks*.

3. Parenteral mercurial therapy is preferable in patients with congested gastrointestinal mucosa, nausea or vomiting, gastric ulcer, or gastritis, who cannot tolerate or absorb oral diuretics.

4. In *recurrent acute left ventricular failure* with paroxysmal nocturnal dyspnea or pulmonary edema, an excellent prophylactic effect can be obtained by a mercurial injection. Such an impending attack, heralded by moderate weight gain, cough, or dyspnea, may be more effectively prevented by a *parenteral mercurial* injection, which acts promptly, than by an oral diuretic which is more slowly absorbed.

5. The intravenous route is rarely indicated except in emergency *situations, such as acute pulmonary* edema or paroxysmal dyspnea, where the advantage of a more rapid response outweighs the possible dangers of toxic reactions. *In such cases*, the mercurial may be combined with aminophylline to relieve bronchospasm and increase cardiac output.

MEASURES TO ENHANCE POTENCY OF MERCURIAL DIURETICS. The effectiveness of mercurial diuresis is enhanced by (1) increased renal blood flow, (2) acidosis or increased pH, and (3) hyperchloremia.

Measures to Increase Renal Blood Flow. The two important measures are *bed rest* and use of *xanthine drugs*. *As already discussed, the cardiac* output and renal blood flow are increased by resting in the recumbent position. Resting for several hours after a mercurial injection may therefore potentiate its effect. In cases where there is massive dependent edema with induration of the tissues, the response to mercurial therapy may be enhanced by *elevation and elastic bandaging* of the edematous lower limbs. This procedure increases the plasma volume and makes more extracellular *fluid available to the kidneys for diuresis*. It should be applied *cautiously after the diuretic* response to the mercurial has begun, to avoid overloading of the venous and pulmonary vessels, and pulmonary edema. Similarly, the xanthine drugs (aminophylline, theophylline) produce a transitory increase in cardiac output. A parenteral injection of *aminophylline* (0.25 to 0.5 Gm) 1 to 3 hr after a mercurial injection may increase renal blood flow and glomerular filtration rate and the diuretic response.

effective diuresis. The acidifying salts potentiate diuresis by producing intracellular tubular acidosis and elevating the serum chloride level, thereby increasing the availability of chloride *for urinary* excretion. The production of hyperchloremic acidosis, by lowering the pH within the renal tubules, facilitates the liberation of mercury ions and enhances the blocking effect on the tubular reabsorption of sodium.

Several types of chloride and acidifying salt have been used *to attain* this effect, including ammonium chloride, calcium chloride, L-lysine and L-arginine monohydrochloride, and acetazolamide. Supplementing mercurial therapy with these acidifying and chloride preparations has become an important clinical measure when the diuretic response to mercurials becomes inadequate and when there is evidence of hypochloremic alkalosis owing to insufficient chloride intake or excessive chloride loss from prolonged diuretic therapy. A poor response to mercurials occurs when the serum chloride level falls below 90 mEq/liter and urinary chlorides fall to 10 mEq/liter or less. The aim of pretreatment with acidifying salts and chlorides

is to enhance diuresis by elevating serum chloride levels to 100 mEq/liter or more and urinary chlorides to 40 mEq/liter or more.

Ammonium chloride is an effective agent for increasing the level of serum and urine chloride ions. The chloride is substituted for carbonic acid in the kidneys, sodium is excreted with the chloride and carbonic acid is retained. The intracellular acidosis and acid urine (pH 5) are temporary, however, and are overcome by increased ammonia production in the kidney, so that in a few days the diuretic effect is gone. Large doses are required, ranging from 6 to 10 Gm daily in divided doses (containing 120 to 200 mEq chloride). Although ammonium chloride is tolerated by most patients, gastric irritation (anorexia and nausea) often develops. Enteric-coated tablets (1 Gm) may reduce gastric irritation but occasionally are not well absorbed. The drug is used intermittently for 3 or 4 days prior to a mercurial injection and then discontinued temporarily to avoid severe acidosis.

Calcium chloride is not well tolerated orally, either, and produces gastric irritation in the required dosage. It can be given intravenously in hypochloremia, in doses of 10 ml of the 25 per cent solution several times daily.

The organic chlorides, L-lysine and L-arginine monohydrochloride, recently have received extensive trial and have been found to be more palatable and better absorbed, producing only occasional diarrhea and abdominal cramps. There is less danger of liver toxicity with these agents than with ammonium salts. Large doses (20 to 40 Gm daily) are required to deliver an adequate amount of chloride to the serum and kidneys. These chlorides are given in four divided doses with cold fruit juices or milk. A dose of 40 Gm contains approximately 200 mEq chloride, which in most cases is sufficient to produce adequate chloruresis, with a rise in the urinary chloride level to 40 mEq or more when given for several days prior to a mercurial injection. In chronic cardiac edema resistant to mercurial therapy, a daily intravenous infusion of L-arginine monohydrochloride (42 Gm/500 ml) for 1 to 3 days, then combined with a daily mercurial injection for 3 days, has been reported to be more successful than oral therapy in producing hyperchloremia and restoration of responsiveness to the mercurial.

Potassium chloride administration, in addition to providing chloride ions, may correct potassium deficiency, which is another cause of decreased response to mercurials. Correction of hypopotassemic alkalosis resulting from previous excessive diuresis or severe heart failure is necessary to restore responsiveness to diuretics and decrease the danger of digitalis toxicity.

Acetazolamide, alone or in combination with ammonium chloride, can also produce hyperchloremic acidosis and potentiate mercurial diuresis. It is given in doses of 500 mg daily for several days and discontinued 24 hr before the mercurial injection so as to avoid an antagonistic effect.

ORAL ORGANOMERCURIALS. Prior to the availability of the thiazide agents, the most potent oral diuretics were the organomercurials, chlormerodrin (Neohydrin), and mercumatilin (Cumertilin). They were widely used for long-term maintenance therapy after the acute heart failure had been controlled with parenteral mercurials and digitalis. Clinical experience up to 1957 (Evans) indicated that the condition of many patients could be controlled with the oral preparations as well as with frequent injections of meralluride.

The effective dose ranges between two and six tablets daily in divided doses, and in severe cases up to eight tablets. Each tablet, containing 18 mg of the organomercurial, is equivalent to approximately 10 mg organic mercury, so that the average daily effective dose contains 40 to 48 mg Hg. However, only 5 to 10 per cent of the ingested mercury is absorbed and excreted, causing uncertain diuretic effects in some cases. Unlike the effect of the carbonic anhydrase inhibitors and the thiouracils, the diuresis is continuous even on long-term administration.

Strict attention must be paid to possible side effects and signs of mercurialism, which may occur not infrequently. These include metallic taste, nausea, abdominal cramps, gingivitis, and colitis. Patients with signs of cardiac decompensation apparently tolerate the drug better than those who are edema-free. Side effects are rare on a dose of three tablets daily or less. Occasionally, even reducing the dose below this level does not eliminate gastrointestinal intolerance. The other toxic effects and contraindications are the same as those listed for the parenteral mercurials.

The oral organomercurials represent a safe and effective method for maintaining continuous and uniform diuresis (Griffith). Although their use has been largely supplanted by the newer oral thiazide derivatives, they should not be discarded, for they still have an important place in long-term maintenance therapy in selected patients. Since their pharmacologic action is mediated through different enzyme systems and their electrolyte excretion patterns differ, the use of these preparations alternately or in combination may be more effective than either one used alone. When excessive potas-

sium excretion occurs with the thiazides, or serious side effects, diuretic therapy can be maintained by switching to an oral organomercurial. This may obviate the use of frequent mercurial injections in ambulatory patients.

Xanthine Drugs. The xanthine agents (theophylline derivatives) act as mild transitory diuretics by their effect on renal hemodynamics. The increase in cardiac output and renal blood flow causes an increase in glomerular filtration rate and makes more filtrate and solute available for tubular excretion. Although there may be a direct tubular effect as well, the primary diuretic action of the xanthines is mediated through their cardiorenal hemodynamic effects There is little danger of renal damage or electrolyte disturbances The xanthines are not sufficiently potent to be used as primary diuretic agents, but the following applications may have clinical value for adjuvant therapy:

Most available parenteral preparations are combinations of mercury and a theophylline agent. The latter, by its effect on glomerular filtration, potentiates the diuretic effect of the mercurial.

A further potentiating effect can be produced by an additional intravenous injection of *aminophylline* (theophylline-ethylenediamine) at the height of the mercurial diuresis (2 to 3 hr after the mercurial injection). Studies have shown a significant increase in renal blood flow, glomerular filtration rate, and sodium excretion by this method To avoid hypotension due to peripheral vasodilatation, the intravenous injection must be given slowly, preferably as a slow drip of 0 5 mg in 250 ml of 5 per cent glucose in water. It is generally given to patients with chronic failure responding poorly to the mercurials Rectal administration in the form of *aminophylline suppositories* (0 5 Gm) or infusion of a solution (0 5 to 1 0 Gm in 100 ml) may give good blood levels but absorption is slower.

Aminophylline intravenously may be used in the emergency treatment of acute pulmonary edema, in which a bronchospastic factor may be important The bronchodilator and cardiac stimulating effects may help to abort the acute attack if used early. Here, too, the injection must be given slowly to avoid hypotensive effects

Oral administration of the xanthines produces only mild transient diuresis unless large doses are used (up to 1 2 Gm daily in divided doses). Such dosage may produce side effects such as nausea, vomiting, and nervousness Several commercial preparations, including *Elixophylline* (15 ml), *Choledyl* (0 2 Gm), and *Aminophylline Dura-Tab* (0.3 Gm), have been introduced in an attempt to minimize these side effects. It is claimed that these agents not only have a diuretic effect but may alleviate episodes of dyspnea They can be used intermittently in mild cases of heart failure, particularly in alternation with the more potent agents to minimize the danger of electrolyte depletion.

Pyrimidines or Cytosine Diuretics (Thiouracils). The *aminouracils* (aminometradine and aminosisometradine), which resemble the xanthines in structure, are mildly potent, oral, nonmercurial diuretic agents. The diuresis (increased excretion of sodium, chlorides, and water) is probably effected by a blocking action on tubular reabsorption. Because of their relatively mild potency and their occasional gastric and other side effects with therapeutic doses (nausea), they have been largely replaced by the more potent thiazide derivatives. However, they may occasionally find a useful place in the therapy of mild heart failure or edema states, especially when the mercurials and thiazides cannot be safely administered or do not produce an adequate response. There are no contraindications to their use, even in the presence of liver or renal insufficiency.

The therapeutic dosage of *aminometradine* (*Rolicton*) ranges between 800 to 1,800 mg daily Starting with 200 mg with each meal, the dosage is gradually increased to 400 to 600 mg per dose until optimum diuresis is achieved; then the dose may be halved. The agent is used intermittently for several-day periods to avoid drug tolerance and loss of potency.

Triazine Diuretics. Chlorazanil (Daquin), a triazine compound, is a mildly potent diuretic with low toxicity, which increases the excretion of sodium chloride and water. The water excretion is relatively greater than that of the electrolytes. Potassium excretion is unchanged or diminished Diuretic action is due to (1) a blocking action on tubular electrolyte reabsorption which differs from that exerted by the mercurials and chlorothiazide, and (2) an antagonistic effect on certain steroid hormones involved in fluid retention. Although it is not much more potent than acetazolamide, it has

the advantage of continued effectiveness on prolonged administration.

A daily dose of 300 mg for several days produces a continuous diuretic response, and if necessary may be increased to 600 mg in divided doses for short-term periods. Prolonged administration of over 300 mg daily, however, may reduce the glomerular filtration rate with impaired renal function (rise in blood urea nitrogen and creatinine, depressed phenolsulfonphthalein excretion). The drug can be used as a supplement or as an alternate to the mercurials or thiazides.

Carbonic Anhydrase Inhibitors. There are two available sulfonamide derivatives, *acetazolamide* (Diamox) and *ethoxazolamide* (Cardrase), which act as mildly potent but nontoxic diuretics. They inhibit sodium reabsorption in the distal tubules by inhibiting the action of carbonic anhydrase, which is involved in the dissociation of carbonic acid to form free H ions. The drug blocks the exchange of hydrogen and sodium ions in the tubular cells, and the interference with carbonate reabsorption results in increased urinary excretion of sodium bicarbonate and potassium but not of chlorides and causes metabolic acidosis. The anhydrase inhibition and increased diuresis are usually transient, lasting for several days only.

These agents have approximately half the relative potency of the thiazide derivatives and one-quarter the potency of the mercurials, and their effectiveness does not improve with increased dosage. A daily dose of 250 to 500 mg is just as effective as a larger dose. Because of the mild potency and development of refractoriness and loss of diuretic effect after 2 to 4 days, they have been largely replaced for oral therapy by the more potent thiazide derivatives.

There are a few special clinical situations in which they may still find a useful place.

1. They may potentiate the action of mercurial diuretics in refractory edema. The hyperchloremia produced by the carbonic anhydrase inhibitors may help to restore responsiveness to a mercurial injection. Diamox or Cardrase may be given for 3 days in doses of 250 to 500 mg daily and then discontinued a day prior to the mercurial injection. After at least 2 days the drug may be started again and the cycle repeated.

2. These agents may augment the diuretic effect of the chlorothiazide derivatives and can supplement them when diuretic response is impaired. Here, too, administration is intermittent, the drug being given daily for 2 or 3 days, or on every second or third day, in doses of 250 to 500 mg daily.

3. It has been claimed that in patients with chronic cor pulmonale and excessive carbon dioxide retention, the increased acidosis produced by the carbonic anhydrase inhibitors may be beneficial by stimulation of the respiratory center. A relatively large dose of 500 to 750 mg daily for several days is given for this purpose.

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The thiazides resemble in structure the carbonic anhydrase inhibitors, but their major pharmacologic action approaches that of a potent organomercurial. Their diuretic effect is based on inhibition of enzyme transport systems in the proximal and distal renal tubules, producing an excretion pattern similar to that of the mercurials by blocking reabsorption of sodium, chloride, and water, but with a significantly greater increase in potassium excretion. These agents produce no significant effects on renal hemodynamics. Their potency is considerable, being equivalent to that of the mercurials, and toxicity is negligible. They are well tolerated orally, with few side effects. Following a therapeutic dose, diuresis begins within 1 hr and reaches a peak effect in about 6 hr. The total effect lasts for about 18 hr, with a range of 12 to 24 hr. Diuretic potency does not diminish with prolonged administration. Saluresis continues with repeated doses until the excess sodium stores and retained fluids are excreted. In the absence of sodium retention the level of urinary excretion of sodium returns to normal in several days.

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These agents have approximately half the relative potency of the thiazide derivatives and one-quarter the potency of the mercurials, and their effectiveness does not improve with increased dosage. A daily dose of 250 to 500 mg is just as *effective as a larger dose* Because of the mild potency and development of refractoriness and loss of diuretic effect after 2 to 4 days, they have been largely replaced for oral therapy by the more potent thiazide derivatives

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ficial effect on edema and other signs of heart failure. The electrolyte excretion pattern seems to be more favorable with the newer agents, particularly the benzylflumethiazide analogues, and chlorphthalidolone, a phthalimidine rather than a thiazide derivative. The sodium to potassium excretion ratio appears to be greater, with less potassium excretion without loss of saluretic and chloruretic effect. However, *potassium depletion* remains an important factor with these agents, particularly following prolonged administration for protracted edema.

CLINICAL APPLICATIONS. The thiazide agents are indicated in all types and in all grades of heart failure. In severe acute failure, it is generally preferable to initiate therapy with injections of a mercurial diuretic daily, or on alternate days for several days. Then, after the main symptoms have been controlled, one can switch to oral therapy with one of the thiazide agents. When the situation is not too acute or urgent, one may start therapy at once with the oral agents. The daily maximum effective dose (Table 18-24) is given in divided doses for the first few days; after a single dose, diuresis may regress after 12 to 18 hr. Also, the diuretic effect is greater with divided doses, every 6 hr, than with one larger daily dose. With all the agents, there is a maximum effective dose above which there is no greater diuretic response. For example, doubling the dose of benzydroflumethiazide from 10 to 20 mg or hydrochlorothiazide from 100 to 200 mg/day *may not significantly increase the 24-hr natriuretic response.* After several days, when edema has diminished and moderate weight loss has been obtained and the weight curve has flattened, the daily dose is reduced to the minimum effective dose required to maintain the weight constant and the patient edema-free. The average maintenance dose (Table 18-24) generally ranges between one-fourth to one-half the dose used in active or initial treatment. If the patient remains edema-free, the dose should be omitted 1 or 2 days each week, to minimize electrolyte disturbances. If signs of edema recur, short intermittent courses of increased doses can be given.

It is important that all the other measures recommended for heart failure be carried out during the stage of active treatment. The indi-

TABLE 18-24 CHARACTERISTICS OF THE THIAZIDE DIURETICS

Thiazide diuretic	*Commercial preparation*	*Potency* *	*Dose, mg*		*Urinary excretion pattern*
			Active treatment	*Maintenance*	
Chlorothiazide	Diuril	0.8	1,000–2,000	250–500	Increased excretion of Na, Cl, and K. Na:K ratio = 3:1. Increased bicarbonate excretion with high doses
Hydrochlorothiazide	Hydrodiuril Esidrix Oretic	1.4	100–200	25–50	Cl excretion greater than Na. Na:K ratio = 5:1
Flumethiazide	Ademol	0.7	1,000–2,000	250–500	Less K excretion at similar dosage
Hydroflumethiazide	Di-Ademil Saluron	1.3	100–200	25–50	Greater Cl excretion than Na. K excretion similar to 3. *Less* bicarbonate excretion
Benzylthiomethyl chlorothiazide (Benzthiazide)	Naclex		100–200	25–50	Na:K ratio more favorable than above. Less bicarbonate excretion
Benzydroflumethiazide	Naturetin	1.8	10–20	2.5–5	Same. Na:K ratio, 7:1
Methylclothiazide	Enduron	1.8	5–10	2.5–5	Same. Na:K ratio, 10:1
Trichlormethiazide	Naqua Metahydrin	1.75	8–16	1–4	Same. Na:K ratio, 6:1
Chlorphthalidolone chlorthalidone	Hygroton	1.8	50	25–50 q.o.d.	Phthalimidine derivative. Excretion pattern same as 8. More prolonged diuresis (over 24 hr)

* Relative to meralluride.

cations for digitalis therapy remain unchanged. Clinical experience has indicated that most patients can be *maintained edema-free* with the combined use of restricted activity, digitalization, and dietary salt restriction. Mercurial injections may be needed periodically if there is recurrence of acute symptoms, but the annoyance of frequent injections is minimized. Also, as previously discussed, rigid restriction *of dietary sodium to 500 mg or less* has become less essential.

With oral daily diuretic therapy, the necessity for using salt-free bread, butter, and milk has diminished. Small amounts of salt can be used in the cooking, depending on the degree *of salt retention and weight gain* observed with *increased salt intake*, and the sodium intake can be gradually increased to 2.0 Gm daily.

TOXIC EFFECTS, PREVENTION AND TREATMENT. As in the case of mercurial diuretics, close observation is essential to detect possible side effects and toxic reactions from the thiazide drugs. This *applies particularly to the* patient on daily maintenance therapy who may not report for reexamination for days, weeks, or even months. The following conditions should be looked for and corrected if present.

Gastrointestinal Irritation. Occasional patients *may develop* nausea, diarrhea, or abdominal cramps. *These symptoms* are aggravated by mucosal congestion in the gastrointestinal tract but may also occur in the absence of visceral congestion. They may be relieved by temporarily discontinuing and then reducing *the dose. Rarely*, the drug has to be discontinued completely.

Skin Eruptions. Pruritus, *paresthesias, and* dermatitis may occur occasionally and may be an indication to discontinue the drug.

Leg Cramps. These may occur, as with any *potent diuretic, when there* is profuse diuresis with excessive loss *of salt. This requires* reducing the size and frequency of the dosage.

Hypotensive Reactions. Occasionally, patients on long-term maintenance therapy may develop orthostatic hypotension with faintness, dizziness, and rarely syncope. These reactions may develop even *when other antihypertensive* drugs have not been administered. In such cases the dosage of all medications must be reduced.

Hyperuricemia. Elevation of serum uric acid levels may occur *occasionally* and is usually asymptomatic. In gouty patients or in those with *latent* gout, it may result in acute exacerbations. If such hyperuricemia is not controlled with *salicylates* and *Probenecid*, the thiazide therapy should be stopped.

Hyperglycemia. Blood sugar levels are occasionally elevated by these drugs. Persons with latent diabetes may develop signs of diabetes (hyperglycemia and glycosuria), and *known diabetic patients may require increase in dosage of insulin or other antidiabetic agents.* Severe diabetic *reactions are rare.*

Renal Damage. The level of blood urea nitrogen (BUN) should be determined periodically in all patients. Mild elevations of blood urea nitrogen may revert to normal *spontaneously* as the failure *improves or with increased* fluid intake. With long-term therapy, however, more persistent elevation of BUN may occur; this is an indication to discontinue the drug. Impaired renal function with *elevated BUN is* rare, and is more likely to develop in patients on severely restricted salt intake with *hyponatremia and hypochloremic alkalosis.* When signs of renal insufficiency and oliguria are present, dietary salt must not be rigidly restricted, and the thiazide drugs should be given with great caution. It would be safer to use intermittent parenteral mercurial therapy rather than continuous therapy with the oral agents.

Electrolyte Depletion. Frequent *serum* electrolyte determinations are indicated in all patients receiving large doses of the thiazide agents for protracted periods. As with the potent mercurial diuretics, severe electrolyte depletion and metabolic imbalance generally *occur in patients with* advanced myocardial disease, protracted *congestive failure*, and deranged cellular electrolyte balance, who have had prolonged and intense diuretic therapy, and in those with previously impaired renal function. The electrolyte disturbances include *hyponatremia*, hypochloremic alkalosis, and *hypopotassemia.*

1. *Hyponatremia.* This is *generally* observed in chronically ill patients with resistant edema and impaired renal function. It is rarely caused *by the* diuretic agent itself. The hyponatremia *is generally* dilutional in type, because of excess water retention, and does not necessarily indicate an excess loss *of sodium, for although* serum sodium is low, the total *body sodium* stores may be increased. This differs from the acute depletional hyponatremia occurring with

restricted salt intake and excessive sodium loss from vigorous diuretic therapy or vomiting. Except in the latter situations, administration of salt solutions is dangerous. Preferably one should discontinue the thiazide drug, restrict fluid intake moderately, and treat with intermittent doses of a mercurial diuretic primed with ammonium chloride or other chloride salt and aminophylline. This may restore a more normal serum sodium level.

2. *Hypochloremic Alkalosis.* This metabolic disturbance is also a manifestation of long-standing heart failure, aggravated by protracted diuretic therapy with chloride-depleting agents. It is an indication to temporarily discontinue thiazide therapy and to carry out the corrective measure for this condition outlined in the section on mercurial diuretics. These measures are essential to restore responsiveness to further diuretic therapy.

3. *Hypopotassemia.* This electrolyte disturbance has become of increasing importance with the ever-increasing use of the potent thiazide agents, which may cause relatively greater potassium excretion than other diuretics. The degree of potassium depletion is related also to the severity of the heart failure, being aggravated by excess aldosterone secretion and reduced sodium excretion Serum potassium levels should be checked in all patients on prolonged therapy. The potassium depletion is less marked with the newer thiadiazine analogues than with chlorothiazide. Despite this, it is desirable to supplement the diuretic therapy with moderate doses of potassium salts, such as potassium chloride (1 to 2 Gm daily) or potassium triplex (5 ml t.i.d) In fact, most of the commercial preparations are now available in a combined tablet with 500 mg potassium chloride, which may be adequate for prophylactic purposes. The diet should be adjusted so as to provide a more liberal sodium and potassium intake High-potassium foods should be included, such as citrus fruits and juices, meat, bran, and milk. When significant hypopotassemia already exists, larger supplemental doses of potassium salts are required and the daily dosage and frequency of administration of the diuretic agent should be reduced.

The two important dangers of severe hypopotassemia are *kidney damage* with impaired renal function and *increased myocardial irritability* The latter may precipitate or aggravate digitalis toxicity in patients on combined digitalis and thiazide therapy. *There appears to be a direct relationship between myocardial concentration of potassium and the dose of digitalis required to produce toxicity.* In acute heart failure, digitalization must proceed more cautiously if the patient is simultaneously receiving large doses of a thiazide drug or other potassium-depleting agent and is excreting increased amounts of urine and electrolytes. Serious *cardiac arrhythmias* may be precipitated by potassium depletion, even before the average toxic range of the digitalis preparation is reached. Similarly, in patients on long-term maintenance therapy with both digitalis and a thiazide agent, strict attention must be paid to dosage of the drugs, dietary potassium and sodium intake, and supplemental potassium administration. In such patients, the minimum rather than the maximum effective maintenance dose of each drug is indicated. The thiazides must be discontinued and oral potassium therapy instituted whenever digitalis toxicity is suspected or there is a significant fall in serum potassium.

When frank digitalis toxicity has developed, larger oral dosage (5 to 7 Gm daily) or intravenous infusion (3 to 4 Gm) of potassium salts becomes necessary, as outlined previously (see Digitalis Toxicity). If continued diuretic therapy is indicated, it would be safer to give intermittent doses of a parenteral mercurial rather than daily doses of a thiazide agent.

Spironolactones. Several years ago, it was observed clinically that the *corticosteroids,* which normally enhance tubular reabsorption of sodium and water and create edema, may exert a paradoxic effect on patients with advanced heart failure and intractable edema by increasing sodium and water excretion (Reimer). Corticosteroid therapy was noted to

filtration rate, inhibition of antidiuretic hormone, and an antagonistic effect on the sodium reabsorption action of aldosterone The latter was considered the most important mechanism.

More recently a new group of *antialdosterone agents* has been introduced, viz, the spironolactones (17-spirolactosteroids). Their use is based on the observation that severe or prolonged congestive failure is associated with a state of secondary *hyperaldosteronism* The ex-

cessive aldosterone excretion increases the reabsorption and retention of sodium and water by the renal tubules, and aggravates the edema state. It has been demonstrated that the spironolactones block the tubular sodium retention and potassium excretion produced by aldosterone. Since the diuretic effect of the spironolactones is mediated by a different mechanism from that of the usual diuretic agents, they should be considered in the treatment of patients with chronic or severe edema not responding well to the usual diuretic regimen.

The available commercial preparation (*Aldactone*), introduced several years ago, has been found to be a useful agent as an adjuvant in the treatment of heart failure, particularly when combined with other therapy. It is available as 100-mg tablets, with a recommended dosage of 300 to 1,200 mg daily (average *100 to 200 mg four times daily*). (*Aldactone A, introduced recently, is available in 25-mg tab*lets, which are equivalent in potency to the 100 mg tablets of Aldactone) Studies during short courses of therapy (7 days) have demonstrated increased urinary output of sodium,

it may be delayed for 1 to 3 days after onset of therapy and then reaches a peak in 2 to 3 days *Drug* tolerance or resistance does not develop with *continued administration* The side effects of the drug are few and mild, such as drowsiness and skin eruptions However, the drug has not been used for sufficiently long periods to indicate its ultimate value and *safety*

CLINICAL APPLICATIONS. *In severe failure re*sistant to mercurials or thiazides, these should be temporarily discontinued, and the patient given 600 to 800 mg spironolactone daily in divided doses A good response is manifested by *increased urinary* excretion and weight loss within 3 to 5 days *of onset of therapy*. The dose can then be reduced to 400 to 600 mg daily for several days or weeks and then replaced by conventional diuretic therapy.

If an inadequate response is observed with increasing doses *of spironolactone* (up to 1,200 mg daily), the therapy is supplemented with an oral thiazide preparation in the usual therapeutic dose or with mercurial injections or both Patients previously resistant to these agents may show a sudden return of responsiveness, with progressive weight *loss and increased* sodium excretion The spironolactone *may* neutralize the *potassium-excreting* effects of these agents, diminishing the dangers of potassium depletion and digitalis toxicity.

In cases of edema refractory to previous intensive therapy, the spironolactone can be added to the diuretic regimen, and the previous measures continued, including the oral chlorothiazide agents, *mercurials, acidifying* and *chloruretic drugs and corticosteroids*. The addition of the spironolactone may produce prompt and gratifying diuresis.

RECAPITULATION OF TREATMENT

The available measures to treat the physiologic disturbances in the heart and kidneys *that are responsible for the manifestations of* heart failure have been discussed. The clinician should be familiar with all of them, so that he can individualize the management of each case, depending upon the type of heart disease present, the precipitating cause of the heart failure, its severity and duration, the type

various pharmacologic agents should vary in cases of mild failure, severe failure, and so-called refractory failure.

Mild Heart Failure. Therapy for mild failure *is as important as for severe heart failure,* since neglect of early *signs of decompensation* may lead subsequently to severe or even irreversible failure. In general, most cases of mild failure can be controlled by restriction of physical stresses, moderate curtailment of salt intake, and slow digitalization followed by minimally *effective maintenance dosage*. As already emphasized, the latter should not be *neglected* in favor of the newer diuretics, since these merely treat the secondary renal manifestations of failure whereas digitalis acts directly on the *impaired* myocardial function to correct the *hemodynamic disturbances*. However, there is no objection to administering *one or more* mercurial injections at the onset or initiating *oral* diuretic therapy immediately with an oral thiazide or organomercurial preparation in *moderate* dosage and continuing with a reduced *maintenance dose* Any one of the preparations discussed can be *given safely* and successfully.

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the primary etiologic factors, are recognized early and the appropriate specific treatment given, if available.

ERRORS IN TREATMENT. One must review the previous therapeutic measures carefully in cases of resistant heart failure to determine if the patient has been undertreated or overtreated.

Undertreatment. Periodically the adequacy of rest, salt restriction, digitalization, and diuretic therapy must be reviewed carefully. If it is suspected that previous management has been inadequate, the patient should be placed at *complete bed rest* and given a carefully supervised low-salt diet (500 mg sodium initially) containing high-potassium foods (fruits and fruit juices, meats, low-sodium milk); the dosage of digitalis and diuretic agents should be increased to the maximum effective levels short of toxicity Various combinations of diuretics, as already discussed, should be tried, as different agents may have additive or potentiating effects.

Overtreatment. Congestive failure may be aggravated by deleterious myocardial and renal effects of overenthusiastic application of salt restriction, digitalization, and diuretic therapy These are common causes for digitalis toxicity and electrolyte-depletion syndromes, which may aggravate the myocardial failure, depress renal function, and produce unresponsiveness to further therapy when the patient has been overtreated with mercurials or thiazine diuretics These must be temporarily discontinued to allow restoration of normal renal function and metabolic and electrolyte balance if possible.

ELECTROLYTE DERANGEMENTS. Careful studies of the serum electrolytes have been emphasized as an essential step in the evaluation of all patients with resistant heart failure. The presence of normal serum electrolytes would suggest that one could continue to pursue a regimen of intensive diuretic therapy. On the other hand, significant lowering of the serum sodium, chloride, or potassium, elevation of blood urea nitrogen, or evidence of alkalosis, would be an indication to temporarily discontinue diuretic therapy in favor of attempts to correct the electrolyte and metabolic derangements that have led to the state of unresponsiveness. All previously described methods must be applied to correct dilutional hyponatremia, hypochloremic alkalosis, and hypopotassemia, if present. The oral or intravenous administration of acidifying and chloruretic agents to elevate serum chloride (above 100 mEq/liter) and to produce an acid urine and increased urinary chloride excretion (above 40 mEq/liter) represents a distinct advance in the correction of hypochloremic alkalosis, which probably is the most important metabolic disturbance in advanced or resistant heart failure, and the one most likely to be the cause of loss of response to mercurial therapy. Alternating or combining the chloruretic agents with potassium salts will have the additional value of correcting or preventing hypopotassemia

Observation of the patient's *response to the* digitalis and diuretic therapy (effect on dyspnea, weight, visible edema, etc.) is important for regulation of dosage and frequency of administration of digitalis and diuretic agents and *determination of degree of restriction of activity* and salt intake required.

Moderate to Severe Heart Failure. In such cases, therapy must be more vigorous. Complete bed rest, oxygen, morphine or other narcotic agents, moderate to severe restriction of salt intake to 1 Gm or less, and rapid digitalization are instituted immediately. An attempt is *made to achieve maximal therapeutic dosage* short of toxicity, with a rapidly acting oral or parenteral glycoside. In previously digitalized patients, dosage should be carefully reviewed to determine if the patient is under- or over-*digitalized, and the digitalis dose should be* adjusted accordingly A program of 3 or 4 days of active diuretic therapy should be started, giving either a mercurial injection daily or on alternate days or a potent oral thiazide preparation in maximum effective doses at 6- to 12-hr intervals. For example, chlorothiazide 1 Gm, or hydrochlorothiazide 100 mg, or benzydroflumethiazide 10 mg, can be given twice daily. If diuresis is inadequate and weight loss too slow, a parenteral mercurial is administered every third or fourth day. Additional diuretic effects can be achieved by such combined therapy When an improved cardiac state is obtained, maintenance therapy is continued with intermittent mercurial injections and a daily oral diuretic, the dosage depending on the severity of residual signs of failure During this early stage, it is wise to obtain determinations of serum electrolytes and other chemistry values, to exclude the presence of electrolyte disturbance or impaired renal function. The findings will dictate the necessity for altering the dietary and diuretic regimen and for other supplementary therapy to correct metabolic and electrolyte derangements These include particularly *hypochloremia* and *hypopotassemia*, which, if present, are responsible for diminished response to diuretic therapy, impaired renal function, and predisposition to digitalis toxicity.

If circulatory congestion and edema persist despite the above regimen, priming of the mercurial agent with acidifying or chloruretic salts is indicated to potentiate or restore diuresis. Ammonium chloride (8 mg daily), or lysine, or arginine monohydrochloride (40 Gm daily), is administered orally for 3 or 4 days, and, on the following day, the mercurial injection is given. Aminophylline (0 5 Gm) may be administered intravenously 1 to 3 hr later or by rectal infusion on the same morning. This cycle can be repeated every 4 to 5 days until a satisfactory loss of edema has been obtained. In severe chronic failure, various other combinations of diuretics can be given a trial, such as thiazides combined with an oral organomercurial, or short courses of a spironolactone combined with a mercurial or a thiazide. Also, *any sizable serous effusion in the pleural or peritoneal cavities should be drained if response to diuretic therapy is slow.*

Resistant or Refractory Heart Failure. Patients with advanced heart disease often reach *a stage when their failure becomes resistant to* the normal therapeutic measures. Such patients must be studied carefully to determine the factors responsible for their refractory state The following factors must be considered as possible causes:

ADVANCED MYOCARDIAL DISEASE Irreversible heart failure may develop in the terminal stages of long-standing myocardial and valvular diseases or in severe acute myocardial damage, as in myocardial *infarction*, *myocarditis*, etc The cardiac reserve is the primary factor which determines whether any form of therapy would be effective in restoring adequate myocardial and renal hemodynamics.

EXTRACARDIAC CIRCULATORY CONGESTION OR OVERLOADING Heart failure with edema and venous congestion associated with *inflammatory*, *circulatory*, hematologic, or metabolic states will not respond to the usual measures without specific therapy for these conditions This includes *steroids* for rheumatic or nonspecific carditis or pericarditis, postmyocardial infarction or postcommissurotomy syndrome, glomerulonephritis, nephrosis, and lupus erythematosus, *thiamine* for nutritional deficiencies or beriberi, *iron and blood replacement* in severe anemias and chronic hemorrhage, *albumin and protein replacement* in hypoproteinemia, *anticoagulants* for recurrent pulmonary emboli, *antibiotics* for myocardial or pulmonary infection or sepsis, *antithyroid drugs or surgery* for hyperthyroidism; and *thyroid* administration for hypothyroidism or myxedema Therapy for heart failure will be unsuccessful unless these conditions, which may be

the primary etiologic factors, are recognized early and the appropriate specific treatment given, if available

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PART 19

Prevention and management of cardiovascular diseases

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7

Electrokymography and other graphic tracings in coronary heart disease

ALDO A. LUISADA AND ALDO JACONO

PHONOCARDIOGRAM

The most typical change observed after a myocardial infarct is the disappearance of the rapid vibrations of the 1st sound. This sound then presents a *prolonged series of slow vibrations* which are *frequently small but may* be of normal height. After the acute stage, it is possible to observe large extra sounds in diastole (*triple rhythm, quadruple rhythm*). These additional sounds are heard only if they are very loud, on account of their low pitch (Fig. 10-20 and 10-23B).

LOW-FREQUENCY TRACINGS OF THE PRECORDIUM

Cardiographic tracings are obtained with difficulty in the acute stage of myocardial infarction because of weak cardiac action. When a good tracing is obtained, a slow development of all waves is usually observed (Fig. *10-20*). This is due to the existence of an area of soft tissue in the left ventricle. By absorbing part of the energy of contraction, this area prevents a rapid rise of pressure and may even cause a less rapid closure of the mitral valve. Therefore, while the 1st sound becomes al-

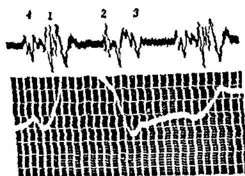


Fig. 10-20. Phonocardiogram (stethoscopic) and low-frequency tracing at apex in a case of coronary heart disease and history of an infarct. Quadruple rhythm. Slow diastolic waves. Slow motion of apex.

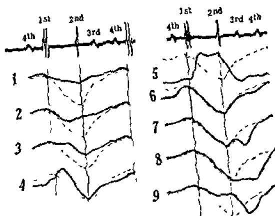


Fig. 10-21. Scheme of the abnormalities of the ventricular EKy (continuous line) compared with the normal tracing (dotted line). 1. Decreased amplitude of contraction. 2. Early end of contraction. 3. Late onset of contraction. 4. Early systolic distention followed by normal contraction. 5. Systolic distention (dynamic aneurysm). 6. Marked presystolic distention. 7. Deep early diastolic rebound. 8. Late systolic distention. 9. Decreased amplitude of contraction and deep early diastolic drop. (From Luisada and Fleischner. Acta. Cardiol. 1948.)

In human beings, the conditions of examination after a myocardial infarction are unfavorable. However, Sampson and Dack described the rapid appearance of dynamic alterations. At the beginning, as a rule, there is a paradoxic expansion; later, during the evolution of the lesions, one or the other of the previous types of changes is observed. Therefore, the functional disorders revealed by roentgen kymography are logically connected with the sequence of structural changes.

The different modifications of left ventricular dynamics represent a wide range, from the simplest (reduction of amplitude) to the more severe (paradoxic systolic expansion). These alterations are usually observed at the apex, but they spread more or less toward the base according to the severity of the case. When two or more types of dynamic changes are observed, the *most severe are always at the apex* In certain cases, the entire left ventricular border is immobile, corresponding to widespread and severe myocardial damage. The oblique positions show the horizontal extension of the dynamic alterations. They are more evident in the RAO position and decrease progressively in severity when the rotation is changed to the LAO position.

In patients with coronary disease, alterations of left ventricular dynamics are observed with great frequency. the author recorded them in 91 per cent of cases (141 times in 155 subjects examined) They are localized in 125 cases (80 per cent) and extended to the entire left ventricular border in 16 cases (10 per cent)

The frequency of the various types of changes is as follows· undulation and reduction, 48 per cent, tremulation, 50 per cent; complete immobility, 56 per cent, paracardiac blurring, 50 per cent; delayed contraction and paradoxic pulsation, more rarely These values are in accord with the findings of Master, Dack, Susmann, and Prinzmetal They are found both in anterior and posterior myocardial infarction The ischemic or infarcted areas localized by electrocardiography do not correspond exactly to the localization of anomalies of left ventricular dynamics because the latter are most often at the apex. This was confirmed by Heim de Balsac and Alessandris in a series of 71 cases of posterior infarction Increased severity of disorders is revealed by the fact that a complete immobility substitutes undulation or reduction of pulsations, on the other hand, even in case of improvement, the paradoxic pulsation is usually irreversible.

The evolution of left ventricular dynamic changes is not strictly connected with that of the electric changes. The amplitude of the contractions may decrease before any other clinical signs; it may follow an evolution parallel to that of ECG changes; or it may evolve in a complete opposite manner. normal dynamics is then found with still abnormal ECG or, on the contrary, persistence of an altered dynamics when the ECG has returned to normal. In the same way, the alterations of ventricular dynamics in patients with coronary disease are not directly related to other signs of altered myocardial function, such as triple rhythm (gallop rhythm) or dilatation of the heart. The roentgen kymographic study of cardiac dynamics supplies important data in coronary diseases, which help, not only for diagnosis, but in order to follow the evolution of the disease Therefore, the author considers left ventricular roentgen kymography as a routine test to be done in all patients with coronary disease. The variations observed are neither surprising or illogical: cardiac dynamics, vibrations revealed by auscultation, changes of intracardiac pressures, and changes of the electric forces are different phenomena, all related to the ventricular activity but not necessarily connected. Therefore, their modifications may be discordants

The study of cardiac dynamics opens the way to new concepts. The observation of larger contractions over the posterior contour of the left ventricle leads to the belief that the left ventricular contraction is not concentric, but has a greater amplitude in a PA plane than in a lateral. The fact that the left ventricle continues to propel blood when all its left border is immobile leads to the belief that, in such cases, the posteroinferior wall and the septum perform all the necessary work. The frequency of the dynamic changes observed at the apex, even in cases of posterior infarction, is more difficult to explain; Master and Dack suggested that it is due to the spiral arrangement of the myocardial bundles inserted on the valvular rings

either the apex or the lateral wall; in 1 case (incompletely studied), a *posterolateral abnormality was found*, in 1, no abnormality. In 7 cases, there was a history of repeated episodes of infarction or of attacks of severe, prolonged precordial pain. In all of them, *marked abnormalities of contraction* were found in the anterior, posterior, and lateral walls The only remaining case had an ECG indicating left ventricular strain, while a large area of the lateral wall of the left ventricle presented abnormalities of contraction These coincidences amount to nearly a 90 per cent identity in the topography of the lesion between the ECG and EKy

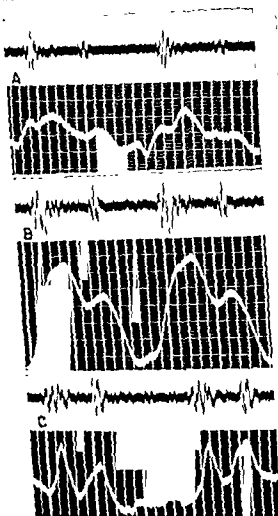


Fig. 10-24 Abnormal pulsations of lateral border in case of posterolateral infarct A EKy of apex, minimal systolic distention. B. EKy above apex severe systolic distention (paradoxical pulsation). C. EKy at upper left border: double pulsation.

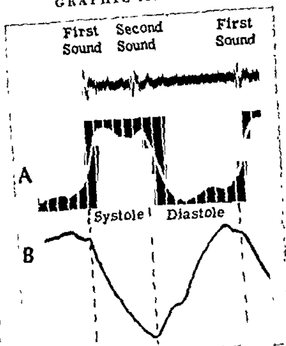


Fig. 10-25. *Old anterolateral infarct with dynamic aneurysm. A Paradoxical, plateau-like expansion in systole. B Scheme of normal pulsation, for comparison (From Luisada, Med. Clin. No. America 1952)*

Some of the abnormalities can be found in other conditions than *myocardial infarction*. For example, a marked *diastolic rebound* was found in acquired valvular lesions and in ventricular septal defects; initial distention followed by contraction was found in certain cases with aortic insufficiency or arterial hypertension Presystolic distention may be found in cases with an atrial type of triple rhythm Therefore, these abnormalities have *no* diagnostic significance in regard to myocardial infarction Some of the diastolic abnormalities are related *directly* to abnormalities of systole and represent a necessary *consequence* of the latter Whenever an inverted movement in early diastole follows an inverted systolic pulsation, it is apparent that it is connected with it and does not deserve *special* mention On the other hand, an inverted diastolic wave can be found as an isolated phenomenon, and then it represents a well-defined and noteworthy abnormality

A *rebound in early diastole represents* a typical abnormality whenever it is *marked* and constitutes a *seemingly* new wave in that phase. The opposite phenomenon is repre-

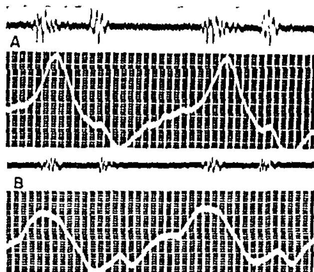


Fig. 10-22. Electrokymogram in a case of antero-lateral infarct. A. Early systolic distention followed by normal contraction at apex. B. Normal dynamics above apex.

tered, all the low-frequency vibrations of the chest also become slow (Fig 10-20).

ELECTROKYMOGRAM

Electrokymography permits an accurate study of the movements of the left ventricular walls and gives tracings which may have diagnostic value.

Various abnormalities have been observed (Luisada and Fleischner; Dack et al, 1950, *Samet et al*) (*Fig 10-21*) Some of them have been found typical of a circumscribed damage to the ventricular wall; others, on the other hand, are not specific and may also be observed in cases with diffuse myocardial damage.

Several abnormal patterns were observed *during systole* Four of them can be grouped together, being an expression of the same phenomenon, i e, a decreased amplitude of the ventricular wave of contraction (Fig. 10-22): reduced amplitude, early end, late onset, or absence of the wave

Two other systolic patterns reveal a more advanced disturbance because they indicate a tendency toward distention (Fig 10-23 to 10-26)· (1) *early distention* followed by a normal ventricular wave, (2) *inverted pulsation* (so-called *paradoxical pulsation*).

In addition to these, a bizarre phenomenon consisting of an M-shaped complex during systole was occasionally observed Various abnormal patterns can also be observed during diastole: (1) marked rebound in early diastole (systolic-diastolic M) (Fig. 10-21); (2) absence of rapid rise in early diastole, (3) drop of the tracing in early diastole, (4) marked distention during presystole

CORRELATION OF ELECTROCARDIOGRAPHIC AND ELECTROKYMOGRAPHIC FINDINGS

Out of 20 cases studied by the authors, 7 were instances of relatively recent myocardial infarction (patients studied within 3 to 6 weeks from the onset of the attack), 8 were instances of old infarctions which had taken place from one to several years previously. The other 5 cases had had repeated infarctions but were also observed within 3 to 6 weeks after a new episode. In 4 cases, the ECG indicated *posterior myocardial infarction;* in all of them, the abnormality of contraction was located in the posterior wall and extended to the lateral wall.

In 8 cases, the ECG indicated *anterior or anterolateral myocardial infarction.* In 6 of them, the abnormality of contraction was located in the anterior wall and extended to



Fig. 10-23. Electrokymogram in a case of antero-lateral infarct. A. "Paradoxical pulsation" (or plateau-like distention) in systole at apex. B. No contraction above apex.

2. *Inverted pulsation (paradoxical pulsation) of a circumscribed area of the ventricular myocardium.* In typical cases, this inverted pulsation assumes the aspect of a *plateau*, indicating that the inert wall is passively distended by intraventricular pressure. This type of pulsation may be associated with the existence of a well-defined bulge of the ventricular silhouette on chest films. In such cases, the name of *ventricular aneurysm* should be used. In other cases, bulging occurs only in systole while no bulge is present in diastole. This phenomenon, occasionally observed on fluoroscopy, is hardly noticeable on roentgenograms, these, even if taken at the maximum of systole, would show but a minute projection, hardly detectable without simultaneous observation of the two opposite motions

It should be kept in mind that the dynamic significance of such an inverted pulsation is similar to that of an aneurysm The wall distends in systole, absorbing part of the dynamic effort of the normal myocardium; it collapses in diastole, disturbing the normal filling and spilling its retained blood into the rest of the ventricular cavity. This similarity, already emphasized by Murray (1947), justifies the term of "dynamic aneurysm" in instances where a typical inverted pulsation is found without any persisting bulge in the profile of the left ventricle It is likely, though not yet demonstrated, that a dynamic aneurysm corresponds to the formation of a "niche" in the ventricular wall, i e, to a remarkable thinning of the wall This fact, which pathologists still call "aneurysm," may not correspond to an aneurysm in a chest film Thus, the EKy is more accurate in its recognition of a severe lesion of the wall than the chest film

Both these typical phenomena, the lack of pulsation and the inverted (or paradoxical) pulsation, were encountered either on the anterior or posterior wall, respectively, or in one of these locations but also extending to the lateral wall, or in a large area including anterior, lateral, and posterior walls The most common occurrence is that of either an anterior or a posterior location with extension to the lateral wall.

Here a remark on terminology may be in order The roentgenologic and electrocardiographic terminologies are not necessarily in perfect harmony. The "anterior wall" of the electrocardiologist is actually "anterolateral." The roentgenologist, on the other hand, calls lateral wall the area adjacent to the profile of the heart silhouette as observed with the patient in the PA position. This profile changes its topographic relation with changes of the position of the heart, such as rotation. From this, it seems quite likely that roentgenologic and electrocardiographic terms overlap each other occasionally and may require reconciliation. As to the extent of the myocardial damage, no strict identity should be expected in electrokymographic and electrocardiographic readings. The deficit in visible muscular activity is not necessarily identical in extent with, and is often larger than, the area of electrical changes.

The above observations reveal functional pulsatory disturbances, and not necessarily irreparable anatomic damage. Repeated observations over a long period of time may reveal return to normal pulsatory function in some instances, while in others, local paralysis or paradoxic pulsations will be persistently observed, indicating irreversible structural damage, probably fibrosis.

The areas of myocardium surrounding the site of occasional damage, as revealed by absent or inverted pulsation, frequently exhibit minor abnormalities They may be due to either functional disturbances at the periphery of the lesion or mechanical repercussion. It is apparent that irregular traction and shaking may occur in the border-line zone between severely damaged and normally functioning myocardium

In general, the findings of electrokymography confirm those of roentgen kymography. However, the electrokymographic method, because of the distinctness and wealth of detail as to timing and configuration of the recorded waves, and the easy approach to the anterior and posterior walls of the left ventricle, permits a better and more accurate evaluation of the various abnormalities.

It is known that, many months after an attack of myocardial infarction, the ECG may revert to normal or may present minor changes, not typical of infarction. Again, it is known that, whenever repeated infarctions take place involving the anterior and posterior walls, the alterations of the T wave indicating the position of the ventricle in which the infarction occurred are often those of the most recent lesion On the other hand, roentgen kymog-

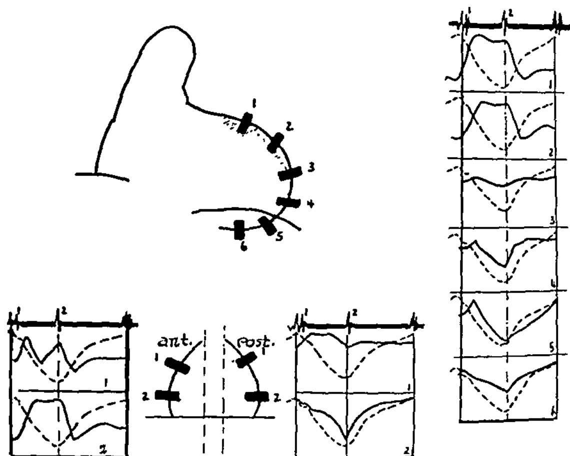


Fig. 10-26. Location of the slit and reconstruction of dynamic changes in a case with multiple infarctions. Large dynamic aneurysm extending from the upper part of the lateral wall to the lower part of the anterior wall. Absence of contraction in the mid-lateral and posterior walls. (From Luisada and Fleischner Acta Card. 1948.)

sented by the *lack of a diastolic return of the tracing toward the base line* This may or may not be connected with abnormalities of the systolic wave. When isolated, this phenomenon is worthy of note and is significant It should be kept in mind, moreover, that some of these deviations from the normal tracing, and particularly those extending over a large portion of the left ventricular contour, are apt to be due to *positional changes* of the heart.

Two abnormalities of ventricular systole, the *late onset* and the *early end of the ventricular wave*, were encountered in cases of infarction but in no other cases, so far. Nevertheless, they should not be considered as having a diagnostic value unless positional changes can be ruled out.

Two abnormalities of the systolic wave have been considered diagnostic of localized myocardial damage, in the majority of instances this being identical with myocardial infarction: [1]

1. *Reduced amplitude of the ventricular wave or disappearance of this wave in a circumscribed region of the left ventricle.*[2] Whenever the surrounding areas present large waves, this sign is definitely related to infarction As that area is functionally (and usually also anatomically) excluded from participating in active contraction, the authors have suggested the name of *local paralysis* for the phenomenon thus revealed by electrokymography

[1] This rule, while undoubtedly true in the great majority of cases, may have its exceptions Myocarditis usually causes *diffuse changes* However, the authors have observed two cases of rheumatic heart disease with valvular lesions in which a localized "paradoxical" pulsation was recorded. In one of them, subsequent autopsy revealed a large patch of fibrosis in the anterolateral wall of the left ventricle caused by old, healed rheumatic myocarditis.

[2] Landowne has remarked that the pattern of "local paralysis" indicates that the damaged area fails to move inward like the rest of the ventricular wall. Thus, it is equivalent to a moderate relative expansion. If this explanation is accepted, "local paralysis" would be equivalent to an initial "dynamic aneurysm."

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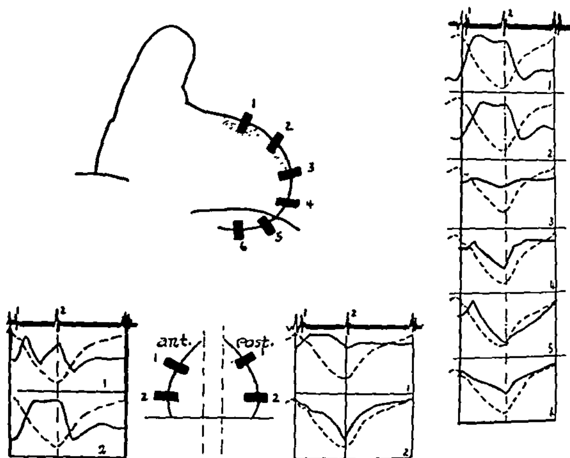


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8

Cardiopexy

SAMUEL A. THOMPSON

Value of Surgery. In myocardial ischemias. and especially in coronary disease, some patients sustain severe myocardial damage and are incapacitated beyond the stage of satisfactory recovery. *Surgery may offer these patients a chance for further rehabilitation which cannot be secured by nonsurgical methods.* During the course of coronary disease, a change from ischemia to hyperemia of the myocardium can give some protection from further serious damage by the ischemic process. *Thus the value of surgery in coronary disease is chiefly that of rehabilitation and protection.*

Principles of Surgery. There are two general principles in the surgical treatment of coronary disease. One is *palliative* and consists in interrupting the nerve pathways through which the painful impulses are carried. The other is *definitive* and consists in the development of an additional blood flow and distribution to the myocardium known as revascularization.

METHODS OF REVASCULARIZATION

Two equally important factors must be considered in correcting myocardial ischemia: they are an *increased* volume of blood and a satisfactory distribution of this blood through the myocardium. Failure to establish either of these will result in failure to correct the ischemia.

The gradual narrowing and final occlusion in coronary artery disease occurs *principally* in the main arteries rather than in the secondary branches, and either the right or left side may be primarily involved. Correcting an insufficient myocardial blood supply and distribution should be aimed at the entire myocardium *and not* at the right or left ventricle. Much of the present-day surgery for the relief of coronary disease is directed toward increasing the blood volume delivered to only one section of the myocardium, namely, the left ventricle, and yet the right ventricle may be the site of the greatest pathologic changes.

Overcoming an inadequate blood distribution because of a blocked coronary system must be done through the growth of new blood vessels or new anastomoses between already existing vessels, such as the communication of extracardiac vesels with the coronary system, distal to the obstruction, and stimulating an increase in the inter- and intracoronary anastomoses.

Sources of Collateral Supply. The source of the additional blood flow may be extracardiac, intracardiac, or a combination of both. The extracardiac source may be from vascular or tissue grafts or from the development of the *residual myocardial circulation.* The term residual myocardial circulation indicates those small blood vessels which actually constitute a preformed source of collateral circulation (Hudson et al.). They have their origin around the base of the heart and great vessels and from the pericardium. When the coronaries become blocked, *they are the principal remaining sources of blood supply.* This circulation is capable of tremendous growth and expansion under proper stimulation, and one of the strongest stimulants is local or surface irritation of the pericardium and myocardium.

A method of increasing the residual myocardial circulation through the pericardium is the *bilateral ligation of the internal mammary*

raphy demonstrated clearly the results of both the recent and old lesions (Gubner and Crawford, 1939; Dack et al., 1940). The authors had the same experience with electrokymography. They had the general impression that the myocardial lesions, revealed by the EKy, were more extensive than those indicated by electrocardiography, since the lateral wall appeared to be involved frequently even in cases of frank "anterior" or "posterior" infarction

While a "dynamic aneurysm" is typical of the scarring of an old infarct, experimental studies (Tennant and Wiggers) and roentgen kymographic observations (Dack et al) indicate the likelihood that a recent infarct also presents this phenomenon.

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arteries just below the pericardiophrenic branches (Battezzati et al.). This produces an increased vascularization of the pericardium. The full benefit of this increased vascularization cannot be utilized unless there is an intimate connection of the pericardium to the myocardium with communication of the pericardial and myocardial vessels below and distal to the coronary obstruction.

USE OF GRAFTS

Many tissues have been used as grafts, but the one tissue which has been most successfully used for a long period of time is the pericardium (Thompson, 1940). The blood supply of the pericardium is abundant and is especially suited because of its proximity. The formation of a granulomatous graft or an area of granulomatous tissue between the graft and host is a valuable addition, provided that this granulomatous area is permanent. In addition to being composed principally of blood vessels, the granulomatous area acts as a bridge through which the extracardiac and intracardiac blood vessels can communicate and through which the vascular continuity can be reestablished proximal and distal to an occlusion.

At the present time the principal vascular graft used is the *internal mammary artery* This operation was devised by *Vineberg*, who has used it successfully for a number of years.[1] However, the greatest increase in the intracardiac blood flow comes through the development of intercoronary and intracoronary anastomoses, giving a more extensive and adequate distribution of the blood This is best accomplished by *surface or local irritation of the myocardium* The importance of irritation is great for irritation produces inflammation and inflammation results in *hyperemia*, which is the reverse of myocardial ischemia Prolonged irritation is better than temporary, and if the irritation is permanent, the best results may be expected.

Another method of myocardial revascularization which utilizes both increased blood supply and distribution is *cardiopericardiopexy* (cardiopexy, for short) This is essentially a form of *permanent surface irritation* and is accomplished by distributing an irritant powder over the surface of the epicardium. This irritant powder (magnesium silicate–U.S.P. talc) is not absorbed by the lymphatics or removed by the phagocytes and results in an area of granulomatous tissue, adherent on its outer side to the pericardium and on its inner side to the myocardium. This granulomatous adhesive area acts as a vascular bridge for the communication of blood vessels of the pericardium and mediastinal structures with those of the coronary system. The irritant also improves the intracardiac blood distribution by stimulating an increase in the number of new vessels to the myocardium beyond the site of the occlusion, as well as an increase in the intercoronary and intracoronary anastomoses. The granulomatous area never changes to scar tissue nor becomes avascular, because the irritant is never removed and it thus acts as a permanent source of collateral circulation The author has been able to demonstrate the permanency of the blood vessels in the granulomatous area as well as the continued presence of the irritant powder crystals by autopsy on patients who have died as long as 10 years after cardiopexy. The technique of cardiopexy has been described in detail (Thompson et al., 1954) and the following is a summary.

The approach to the heart is over the fifth left costal cartilage, which is removed. This approach is used because the pericardium is exposed without entering the pleural cavity. After a small opening is made in the pericardium, all fluid is aspirated to prevent the powdered talc from being washed to the dependent recesses of the pericardium The irritant powder is then widely distributed over the anterior surface and borders of the myocardium No attempt is made to cover the posterior surface as some of the powder is carried there by the beating action of the heart The pericardial opening is loosely closed, and the chest wall structures are closed in anatomic layers without drainage.

This procedure is simple, has a low mortality, and can be used in severely handicapped patients. The addition of bilateral ligation of the internal mammary arteries may further increase the good results of cardiopexy.

Another method of myocardial revascularization is the one used by Beck since 1950 This is *a combination of surface irritation plus a partial occlusion of the coronary sinus* The surface irritation is produced by mechanically scarifying the lining epicardium of the pericardium and myocardium. This is followed by

[1] See Chap. 9. *Editor.*

the application of asbestos fibers scattered over the raw areas. The partial occlusion of the coronary sinus is done by an encircling ligature tied down over a 3-mm probe Beck and Brofman (1956) report very satisfactory results with this method.

BENEFITS

The benefits from cardiopexy are rehabilitation, protection, and increase in life span. Rehabilitation comes through relief of pain and improvement in the exercise tolerance. There is protection from fear of the agonizing precordial pain coming on at unpredictable times of the day or night. There is also some protection from the fear of possible sudden death, as less than 1 per cent of cardiopexy patients (who survived the operation for as long as 3 months) have died suddenly The percentage of sudden deaths in the unoperated cases of coronary disease is much higher A study of the patients who have died subsequent to a cardiopexy and a comparison with groups of unoperated patients with coronary disease who have died leads us to believe that the life span of the operated patients averaged more than 5½ years longer than the unoperated patients

TESTS OF REVASCULARIZATION

Evidence of revascularization can be seen by the following five tests

TESTS FOR MYOCARDIAL REVASCULARIZATION

1 *Intercoronary—peripheral coronary backflow* following a central occlusion
2 Extracardiac—retrograde aortic filling of coronary arteries
3 Continued myocardial contraction in the zone of an occluded coronary artery
4 Failure of myocardial contraction when the collateral flow is removed
5 Tests of clinical improvement

The peripheral coronary backflow represents the basal intercoronary anastomosis Retrograde aortic filling of the coronaries by this maneuver is definite evidence of extracardiac anastomosis Myocardial contractions cease when the blood flow is cut off The clinical tests include relief of precordial pain, increase in exercise tolerance, performance of daily duties, and a return to some gainful occupation

The first is a test of *intracardiac collateral blood flow* as measured by the peripheral coronary backflow in both quantity and oxygen content following a central occlusion In the normal animal, the volume is about 1.7 *ml/min* Following cardiopexy, this volume is increased *to* 5 3 *ml/min* Bakst).

The second test is for *extracardiac collaterals* and is done by placing a clamp over the ascending aorta just above the origin of the coronaries, a second clamp is placed just above the diaphragm. This isolated section *of aorta is* then injected with a colored opaque solution of plastic material. In the normal animal, the coronaries are not filled by this maneuver. Following cardiopexy, this test shows filling of the coronaries in 50 per cent of the animals and is definite evidence of extracardiac anastomoses (Bakst).

The third test is *continuation of myocardial contractions in the zone supplied by an occluded coronary artery*. In normal animals, following complete occlusion of the anterior descending coronary artery, there was about a 50 per cent mortality from ventricular fibrillation or infarction. When the same occlusion *is done 2 weeks after cardiopexy*, the mortality is zero (Gregg and Dewald).

Failure of myocardial contraction when the source of the collateral flow is removed is the fourth test. In a group of animals who had a preliminary cardiopexy, a series of operations was performed in which both coronaries were ligated up to their origins Then, as a last procedure, the adherent pericardium, through which the collateral flow came, was removed, and none of the animals survived.

Clinical improvement of the patient is the fifth test While this test may be considered subjective *by some, it is certainly the most important in so* far as the patients are concerned This is measured by the relief in pain, the improvement in physical exercise tolerance, the ability to perform daily duties, and the return to a gainful occupation.

These five tests appear to give conclusive evidence of myocardial revascularization Any patient with coronary disease, with or without *a previous infarction*, who remains physically incapacitated as much as 50 per cent because of pain or dyspnea, should be considered as a candidate for surgery. The two principal contraindications are an acute or unhealed infarction and intractable congestive failure.

RESULTS

Cardiopexy was devised and first performed by the author in 1938, and that first patient is still living Since that time, the author has operated upon and observed over 400 patients. The following data shows the results: there is an operative and hospital mortality of approximately 5 per cent Using the clinical tests described above, 10 per cent of the patients have

arteries just below the pericardiophrenic branches (Battezzati et al.). This produces an increased vascularization of the pericardium. The full benefit of this increased vascularization cannot be utilized unless there is an intimate connection of the pericardium to the myocardium with communication of the pericardial and myocardial vessels below and distal to the coronary obstruction.

USE OF GRAFTS

Many tissues have been used as grafts, but the one tissue which has been most successfully used for a long period of time is the pericardium (Thompson, 1940). The blood supply of the pericardium is abundant and is especially suited because of its proximity. The formation of a granulomatous graft or an area of granulomatous tissue between the graft and host is a valuable addition, provided that this granulomatous area is permanent. In addition to being composed principally of blood vessels, the granulomatous area acts as a bridge through which the extracardiac and intracardiac blood vessels can communicate and through which the vascular continuity can be reestablished proximal and distal to an occlusion.

At the present time the principal vascular graft used is the *internal mammary artery* This operation was devised by *Vineberg*, who has used it successfully for a number of years.[1] However, the greatest increase in the intracardiac blood flow comes through the development of intercoronary and intracoronary anastomoses, giving a more extensive and adequate distribution of the blood This is best accomplished by *surface or local irritation of the myocardium* The importance of irritation is great for irritation produces inflammation and inflammation results in *hyperemia*, which is the reverse of myocardial ischemia Prolonged irritation is better than temporary, and if the irritation is permanent, the best results may be expected

Another method of myocardial revascularization which utilizes both increased blood supply and distribution is *cardiopericardiopexy* (cardiopexy, for short). This is essentially a form of *permanent surface irritation* and is accomplished by distributing an irritant powder over the surface of the epicardium This irritant powder (magnesium silicate–U.S.P. talc) is not absorbed by the lymphatics or removed by the phagocytes and results in an area of granulomatous tissue, adherent on its outer side to the pericardium and on its inner side to the myocardium. This granulomatous adhesive area acts as a vascular bridge for the communication of blood vessels of the pericardium and mediastinal structures with those of the coronary system. The irritant also improves the intracardiac blood distribution by stimulating an increase in the number of new vessels to the myocardium beyond the site of the occlusion, as well as an increase in the intercoronary and intracoronary anastomoses. The granulomatous area never changes to scar tissue nor becomes avascular, because the irritant is never removed and it thus acts as a permanent source of collateral circulation The author has been able to demonstrate the permanency of the blood vessels in the granulomatous area as well as the continued presence of the irritant powder crystals by autopsy on patients who have died as long as 10 years after cardiopexy. The technique of cardiopexy has been described in detail (Thompson et al., 1954) and the following is a summary.

The approach to the heart is over the fifth left costal cartilage, which is removed. This approach is used because the pericardium is exposed without entering the pleural cavity. After a small opening is made in the pericardium, all fluid is aspirated to prevent the powdered talc from being washed to the dependent recesses of the pericardium. The irritant powder is then widely distributed over the anterior surface and borders of the myocardium No attempt is made to cover the posterior surface as some of the powder is carried there by the beating action of the heart. The pericardial opening is loosely closed, and the chest wall structures are closed in anatomic layers without drainage

This procedure is simple, has a low mortality, and can be used in severely handicapped patients. The addition of bilateral ligation of the internal mammary arteries may further increase the good results of cardiopexy.

Another method of myocardial revascularization is the one used by Beck since 1950 This is *a combination of surface irritation plus a partial occlusion of the coronary sinus*. The surface irritation is produced by mechanically scarifying the lining epicardium of the pericardium and myocardium. This is followed by

[1] See Chap. 9 *Editor.*

9

Surgery of coronary heart disease

ARTHUR M. VINEBERG

The treatment of coronary heart disease by medical or surgical means has been and still is most difficult—as well as unsatisfactory. This is attested to by the ever-increasing mortality and morbidity of the disease, which is now responsible for at least one in four deaths that occur in North America

As the disease is said to be unpredictable in its course, any form of treatment is difficult to evaluate. It has, in fact, been stated that "almost anything may cure precordial pain" This statement would be correct if it were modified to read, "almost anything may bring about temporary relief from precordial pain"

Credit for beneficial treatment, whether medical or surgical, has frequently been based upon sketchy pre- and postoperative evaluation of a patient's disease There are many reasons for this situation, mostly based upon misunderstanding, disagreement, and confused thinking. In this chapter, some of the thinking about the treatment of coronary heart disease will be reviewed so that, wherever possible, generally accepted facts may be listed, and the role of surgery in the treatment of coronary heart disease examined in their light

CORONARY CIRCULATION IN HEALTH AND DISEASE

The coronary circulation is different from that of any other circulating system in the human body It is necessary for all students of coronary heart disease to understand something about the complexity of the structure and function of the heart of man and lower animals In the past, there have been many disagreements concerning the character of the coronary circulation, particularly in reference to the anatomic vascular channels that lie within the ventricular myocardium and to their connections between the coronary and mediastinal vessels. During the past few years, a clearer picture has emerged, so that now there are certain facts about which there appears to be general agreement.

Two large arteries leave the aorta just above the right and left aortic cusps to form the main right and left coronary arteries, respectively.[1] The left coronary artery divides into the anterior descending septal and circumflex coronary branches. These large coronary arteries lie on the surface of the heart beneath the epicardium. Each large artery supplies a separate zone of arterioles lying within the myocardium Under normal conditions, there is little or no connection between the myocardial arteriolar zones supplied by the four major coronary arteries, it is for this reason that for many years the coronary arteries were considered to be end arteries [Fig 10-26(1)]. This view was tenable until Schlesinger and Zoll, through radiopaque injection studies of human coronary arteries, demonstrated the presence of numerous arteriolar-size branches running between different coronary arteriolar zones They found these communications to exist when there was narrowing or occlusion of coronary arteries in their epicardial courses. These types of communication between arteriolar zones or between arteries have been termed "collaterals" and have been shown to exist in 9 per cent of normal human hearts and in practically all human hearts with evidence of myocardial ischemia caused by coronary artery narrowing.

The "Collateral," Its Development and Distribution. For years physicians have been saying that if a patient is given time, he will develop his own collaterals and thus heal himself, further, that

[1] See Part 1, Chap. 6. *Editor.*

not been improved by as much as 50 per cent, and this is considered a poor result. The remaining 90 per cent of the patients show a minimum of 50 per cent improvement, and this is considered a good result. Some of the patients (40 per cent) are improved more than 75 per cent, and this is considered as an excellent result. Almost all the patients had sustained infarctions before the operation, and the vast majority were almost completely incapacitated.

In summarizing the surgical treatment of coronary disease and myocardial ischemias, two general principles are involved. One is palliative and consists of neurosurgical procedures. The other is definitive and consists in methods of myocardial revascularization. One of the simplest of these is cardiopexy. The mortality is low, and a 21-year follow-up shows the results are not surpassed by any other method.

In conclusion, it appears evident that the benefits to be obtained from surgery in cases of coronary disease and myocardial ischemia are rehabilitation, protection, and the prolongation of life.

arteriolar collaterals have developed to aid a more even distribution of blood throughout the heart muscle.

The problem thus resolves itself into a mechanical hydraulic one Coronary arteries *supplying blood to an area* of the myocardium have a well-established cross section which permits a maximum quantity of blood to flow through their channels into that area. It has been said that occlusion of one major coronary *artery* is necessary *to produce precordial* pain. It is evident that if one major coronary artery is occluded and another artery is somewhat narrowed, the third coronary artery cannot supply *the* amount *of* blood formerly *supplied by* the blocked *and narrowed* vessels This situation, therefore, results in either progressive slow death of the myocardium or sudden death in the form of myocardial infarction

The point of critical *coronary* artery *narrowing* has been clearly substantiated in the experimental laboratory at McGill University. It has been shown in animals that when two major coronary arteries, the anterior descending and circumflex arteries, are narrowed by ameroid constrictors to 50 per cent or more of their average lumens, the animals will die within a 28-day period In roughly 15 per cent of the animals, there is a large connection between the right and left *coronary arteries. In such* instances, the animals may survive partial constriction of their two major left coronary arteries. It is thus clear that ischemia in the human or animal heart stimulates *only the collaterals that lie* between the arteriolar zones and *between* coronary

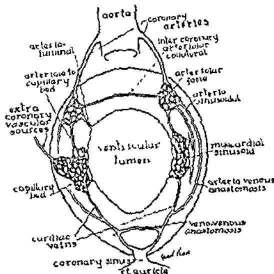


Fig. 10-26(4). *Myocardial circulation.*

arteries. There is no *evidence to indicate that in the diseased* human heart, *or in* the animal *heart* artificially made ischemic, there is an ingress of extracardiac arteriolar-sized blood channels into the myocardium.

The Myocardium as a Vascular Sponge. The vascular structure *of the myocardium* has been the subject of much controversy over the past 75 years Debate has centered on the existence or absence of (1) vessels in the heart walls communicat*ing* with the heart chambers; (2) vascular spaces *lying between myocardial fibers*, other than the capillary system.

Wearn, in a brilliant piece of work, clearly defined the relationship of thebesian arteriolumnal vessels *and myocardial sinusoidal spaces*. His conception of the vascular structure of *the myocardium* has been confirmed by others, including the author [Fig 10-26(4)] The concept of Wearn and the author concerning the structure of the coronary circulation, *if correct, permits of the theory* that the myocardium may obtain oxygenated blood from two sources, viz., (1) the coronary arterial tree, (2) the lumen of the ventricle. It is theo*retically possible for the* blood to be siphoned back into the ventricular wall *through arteriolumnal* and myocardial sinusoidal spaces during diastole, when such spaces are empty. This can happen *only in the diseased heart*, where there is little or no forward flow *into the myocardium* through the narrowed coronary arteries During *systole*, the vascular spaces of the myocardium are emptied by the squeezing action of the myocardial fibers and the blood is moved into the venous system [Fig 10-26(5)].

Myocardial sinusoidal spaces have *been frequently* shown in the author's laboratory. Because

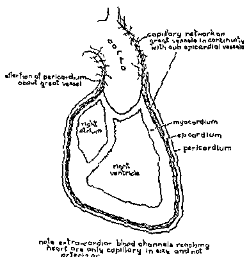


Fig. 10-26(3). *Type and course of mediastinal vessels entering heart.*

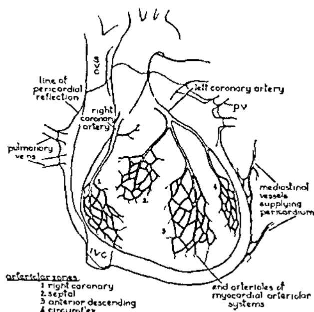


Fig. 10-26(1). Coronary artery distribution into separate arteriolar zones in normal heart.

patients have been known to live without any open coronary arteries whatsoever It is at this level that much clarification is needed

What do clinicians mean when they speak of "collaterals"? The majority of them picture blood vessels, from somewhere, reaching the ischemic areas of the myocardium This view is correct when it is confined to the opening up of communications between neighboring arteriolar zones within the confines of the heart, either upon its surface or within its musculature [Fig 10-26(2)]. It is badly founded when it suggests that extracardiac vessels of arteriolar size are capable of reaching the myocardium Both physiologists and pathologists have drawn attention to the blood vessels that reach the heart in the region of the pericardial reflection around the great vessels as they leave and enter the heart It has been suggested that collaterals may be established between the pericardial blood vessels and the heart via these routes

Evidence for the Presence of Extracardiac Channels. EPICARDIUM [2] The epicardium is composed of a thin layer of mesothelium, a simple squamous or cuboidal epithelium, together with a subjacent layer of fibroelastic connective tissue

CONNECTIVE TISSUE The connective tissue of the epicardium contains a considerable amount of fat, particularly in the region of the sulci and around the layer of vascular channels that lie over the surface of the ventricles It is continuous with the connective tissue forming the serosa of the great vessels entering and leaving the heart The deep layer of the epicardial connective tissue is continuous with the perimysium of the myocardium The perimysium is a dense layer of fibroelastic connective tissue that surrounds groups of muscle fiber bundles. In this layer is a network of blood and lymph capillaries and myocardial sinusoids.

There is thus no doubt that there is anatomic continuity between the capillaries of the serosa of the great vessels and those of the deeper layer of the epicardium. Many injection studies have shown connections between mediastinal vessels and the subepicardial vessels that reach the heart around the great vessels. These mediastinal myocardial-vascular connections have been frequently described, however, they have all been demonstrated by the injection of india ink or other fluid materials, and such injection studies prove very little except that a capillary network of vessels exists between the extracardiac vessels and the coronary vessels [Fig. 10-26(3)].

Of the numerous injection studies made by Schlesinger and Zoll, Blumgart and Zoll, and more recently by May, and others, there is no recorded evidence of arteriolar-size connections between the coronary arterial tree and the mediastinal vessels and the tissues surrounding the vessels that leave and enter the heart of man and animals. This is true of the human heart whether normal and healthy or diseased

The term "collateral vessel," therefore, must be reserved for arterioles that connect coronary arteriolar zones within the myocardium, it cannot be used to suggest the presence of, or the development of, extracardiac coronary arteriolar anastomoses.

The acceptance of this anatomic, pathologic fact makes it clear that *the myocardium can exist only on blood supplied by its own coronary arterial tree*

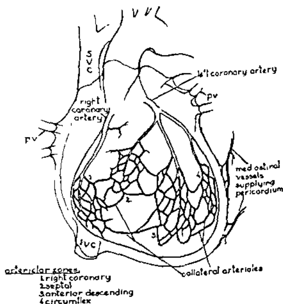


Fig. 10-26(2). *Arteriolar collateral development in ischemic heart*

[2] See Part 1, Chap. 5 *Editor.*

THE HEART The effect of coronary artery disease upon the heart is related to many factors, a great number of which are still unknown, and others unexplained. The myocardial fiber, which fundamentally is the unit of life, requires oxygenated blood in varying amounts. When a segment of myocardial fiber suffers diminution of blood supply because of narrowing of the supplying coronary artery, the area becomes anoxic. This may go unnoticed by the patient and, if it progresses, may result in the death of the affected area, forming a silent myocardial infarction. In most cases, however, the patient receives a warning of the area of myocardial ischemia and experiences precordial pain.

It is safe to say that precordial pain is generally accepted as a symptomatic reflection of myocardial ischemia caused by coronary artery insufficiency, and that when it occurs at least one major coronary artery is severely narrowed. When precordial pain persists in spite of medical therapy, there is no agreement as to the extent of myocardial fiber damage that may result. In the author's opinion, persistent precordial pain reflects continuous myocardial ischemia which results in progressive destruction of myocardial fibers.

Hill has shown that the longer the history of precordial pain is, the poorer the operative risk is and the less likelihood there is of a good result after revascularization.

Progressive destruction of myocardial fibers, whether due to chronic ischemia or to repeated acute myocardial infarction, usually leads to left ventricular failure. It may result in ventricular aneurysm, ruptured papillary muscle, or interventricular septal defect.

VENTRICULAR FIBRILLATION Another possible result of severe hypoxia or anoxia of the myocardial fiber is ventricular fibrillation. It has been shown by Beck that a small area of anoxia in the ventricular myocardium is sufficient to send the heart into ventricular fibrillation, with resultant death, unless the heart can be immediately defibrillated. Beck has frequently stated that these hearts "are too good to die." Immediate defibrillation has resulted in the resuscitation of a great number of patients who are living normal lives several years later.

Excluding the question of endocardial nutrition, the facts just mentioned have been proved by many and are now generally accepted.

SURGICAL PROCEDURES FOR THE TREATMENT OF CORONARY ARTERY DISEASE

Operative procedures are designed to (1) increase myocardial circulation, or (2) correct mechanical defects resulting from myocardial



Fig. 10-26(7). Myocardial sinusoidal space filled by injecting with india ink a human internal thoracic artery.

ischemia, such as left ventricular aneurysm, ruptured papillary muscle, or ruptured interventricular septum.

In the first group, it seems best, from a practical point of view, to list the various procedures under general headings according to the theoretical concept of their intended action and effect. These procedures are as follows.

SURGICAL PROCEDURES DESIGNED FOR THE CORRECTION OF CORONARY ARTERY INSUFFICIENCY

I Extracardiac procedures for pain relief
  A Neurosurgery to block afferent pain pathways
    1 Cervicothoracic ganglionectomy (Jonnesco, 1916)
    2 Chemical nerve block (Swetlow, 1926)
    3 Posterior rhizotomy (Hoven and King, 1942)
    4 Pericoronary neurectomy (Fauteux and Swenson, 1946)
  B Reduction of general metabolism
    1 Total thyroidectomy (Blumgart and Levine, 1933)
    2 Radioactive destruction of the thyroid gland
II Development of collaterals, anastomoses, or both
  A Ligation of cardiac vein (Fauteux, 1940)
  B. Ligation of coronary sinus (Gross and Blum, 1935)
  C Bilateral ligation of internal thoracic artery
  D Epicardiectomy and Ivalon sponge operation (Vineberg)
III Procedures to increase myocardial blood supply
  A. Bypass operations
    1 Myocardial vascularization by extracardiac blood

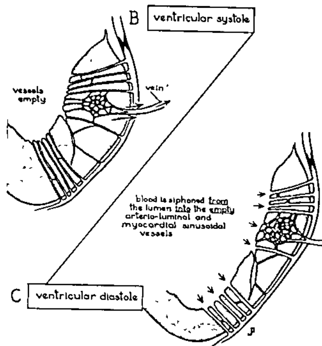


Fig. 10-26(5). Mechanism by which the vascular spaces of the myocardium are emptied and the blood is moved into the venous system

they exist, it has been possible to implant an open and bleeding systemic artery into the myocardial tunnel without formation of a myocardial hematoma. This has been performed many hundreds of times in the author's laboratory using the internal mammary artery. Others have had similar experiences with the splenic, carotid, or subclavian arteries. Such myocardial systemic arterial implants remain open because there is a satisfactory run-off through the myocardial sinusoidal and perhaps arterioluminal channels. A schematic drawing of such a mechanism is shown in Fig. 10-26(6). Figure 10-26(7) shows a myocardial sinusoidal space filled by injecting a human internal mammary artery, 82 hr after implantation, with india ink.

Surgical Pathology of Coronary Heart Disease. In surgery for coronary heart disease, consideration must be given to two major parts of the heart: (1) the part pertaining to the coronary arterial system, which perhaps may best be called *the myocardial circulation;* (2) *the heart itself,* in which the myocardium, the valves, and the papillary muscles may have become damaged.

THE CORONARY ARTERY SYSTEM AND THE MYOCARDIAL CIRCULATION. Atherosclerosis is a major disease affecting the coronary arteries. One rarely sees syphilitic aortitis which involves the coronary ostia. There are, however, other causes of coronary artery disease and of myocardial ischemia that are beyond the scope of this article. There is general agreement that atherosclerosis involves the arteries largely in their epicardial courses, leaving a vast arteriolar network within the myocardium comparatively disease-free.

Patients with severe diabetes and hypertension are the exception to the rule. In such patients, the smaller arterioles within the myocardium are much more likely to show atherosclerosis than in other patients without these two conditions.

A study of the distribution and extent of coronary artery atherosclerosis reveals that from 13 to 18 per cent of cases examined have segmental disease, i.e., isolated areas of occlusion or narrowing. These studies have been made at autopsy. It is probable that if more detailed coronary arteriography were available, the incidence of segmental coronary artery disease would be found to be higher, particularly in the younger age group.

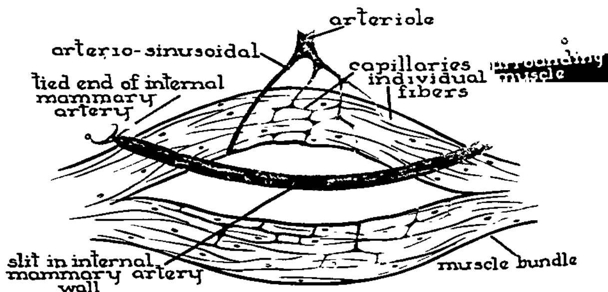


Fig. 10-26(6). Mechanism of internal thoracic artery branching within the myocardium.

results of these procedures are difficult to evaluate because the neurosurgical reports deal largely with pain, its relief, and neurosurgical techniques. Very little is mentioned in regard to the type of condition for which the patient is operated upon.

CERVICOTHORACIC GANGLIONECTOMY. Lindgren treated 105 patients by cervicothoracic ganglionectomy (*operative mortality, 8.5 per cent*). The anterior *approach* was used in *stages* 2 months apart; the stellate and upper T_4 and T_5 ganglia were removed bilaterally. Pain was relieved in 75 per cent of patients, with 66 per cent reporting an increased capacity for work. A warning signal still remained. There was no evidence *of prolongation of life.*

POSTERIOR RHIZOTOMY. This procedure involves section of the posterior sensory nerve roots and of the upper four or five thoracic nerve roots.

White reports 31 cases collected from different centers, with 3 *operative deaths,* and with complete relief of pain in all but 2 patients. The advantages of this procedure are the following: (1) there is no possibility of regeneration; and (2) the fibers can be cut at both ends at the same operation. The disadvantages are (1) *it is a major procedure on* bad-risk patients, (2) bilateral laminectomy involving four vertebrae, a time-consuming procedure, is necessary, (3) there is danger of ischemia, transverse myelitis, and anoxia owing to the prone position.

PERICORONARY NEURECTOMY. This procedure involves *paravertebral alcohol injection* of the upper thoracic sympathetic ganglia.

> White has treated 77 patients with precordial pain with 100 alcohol injections, with *no major or serious complications.* He reports that 62.3 per cent of patients experienced complete relief of pain on the side of denervation, 20.8 per cent were improved, 7.8 per cent of the *attempts failed,* and there was a 9.10 per cent death rate. In the hands of others, chemical block of afferent pathways has *not been so successful.*

The disadvantages of this procedure are as follows. (1) it has failed to control pain in at least 10 *per cent of cases* and there has been an 18 per cent recurrence rate within 2½ months, (2) the injections, started *under local* anesthesia to detect Horner's syndrome and outline the absence of sweating, may be painful, (3) spinal cord surgery may produce a resultant myelitis; (4) deaths have occurred; (5) intercostal neuralgia may be *troublesome* and may last a long time.

> White suggests use of cardiac denervation for precordial pain in the following groups of patients: (1) those with severe "angina decubitus," to forestall drug addiction and give some relief, (2) those *who cannot* tolerate hyperthyroidism; (3) those with aortic insufficiency and syphilitic aortitis who have precordial pain.

Certainly the paravertebral injections of alcohol, as carried out by White, seem to be worthwhile in bed-rest patients with severe precordial pain.

Development of Collaterals, Anastomoses, or

Both

tion

bilat

Gross ... nary sinus ligation would hasten the physiologic process of aging by the formation of collaterals. Both the procedures of great cardiac vein ligation and coronary sinus ligation in the treatment of coronary artery disease are based *upon this concept.*

Fauteux (1939–1940) reported *a protective* effect against anterior descending branch ligation after cardiac vein ligation, which persisted up to 1 year in animals; in 1946 he reported his results in 10 patients with precordial pain, 7 of whom had returned to work. Ripstein *(1948) analyzed* the results of 40 cases and reported that 72 *per cent* of the group had benefited from the procedure.

LIGATION OF CORONARY SINUS. Total ligation of the coronary sinus *frequently* causes marked venous congestion and turgidity of the ventricular wall. For this reason, Beck modified *the operation by tying* the coronary sinus at its entrance to the right *atrium around* a 3-mm probe. Beck is of the opinion that by *this* means, intercoronary collaterals are opened and a wider distribution of blood is brought about throughout the ventricular myocardium. In the past *few years,* he has performed this operation upon patients suffering from coronary artery insufficiency. The *partial ligation of the coronary sinus* is supplemented by *abrasion of the epicardium and inner surface of the pericardium* with a mechanical abrader and by the introduction *of* asbestos powder between the heart and the pericardial fat pads that are sutured directly to the heart muscle. This operation is

2. Surface grafts
   a. Pectoral muscle (Beck, 1935)
   b. Omentum (O'Shaughnessy, 1936)
   c. Lung (Lezius, 1937; Carter, 1949)
   d. Lung and ligation of pulmonary artery (Liebow, 1950)
   e. Pericardial fat pad (Vineberg, 1954)
   f. Skin (Moran, 1952)
   g. Jejunum (Key, 1954)

B. Arterialization of coronary sinus (Beck, 1948)

C. Cardiopericardiopexy
   1. Bone, chips, asbestos, etc (*Feil and* Beck, 1937)
   2. Talc (Thompson, 1939)

D. Ventricular arterialization by vascular implants
   1. Internal thoracic artery implant (Vineberg, 1946–1961)
   2. Splenic artery implant (Liebow, 1956)
   3. Carotid artery implant (Sabiston and Blalock, 1956)

E. Graft from aorta to myocardium
   1. Single (Vineberg and McIntosh, 1954–1957; Sabiston and Blalock, 1956; Smith, 1957)
   2. Double (Vineberg and Duchesne, 1957)

IV. Myocardial circulation from the left ventricular lumen
   A. Epicardiectomy
   B. Epicardiectomy and Vineberg sponge operation
   C. Direct tapping of left ventricle (Vineberg-Massino)

V. Direct attack upon the coronary arteries
   A. Endarterectomy (May, Bailey, Sabiston, Longmeyer)
   B. Endarterectomy with patch graft (Senning)
   C. Resection *segments with end-to-end anastomoses* with or without graft (Robb)
   D. Systemic artery to distal end of coronary artery (numerous workers)

From the above list, it is evident that many different attempts have been made to treat coronary heart disease surgically. A careful examination of the experience with each procedure reveals the shocking fact that few of them have had adequate experimental background before their application to human beings. The author has frequently stressed the importance of the experimental laboratory in assaying a surgical procedure. This view has not been and is still not universally held. Yet those who criticize animal experimental evidence as being *valueless because of the differences* between human beings and lower animals are the first to try out a new surgical procedure based on a theoretical but unproved concept. It is quite true *that that which is of value in an animal may* not be of value in a human being, it is just as true, however, that a procedure that has not worked in a lower animal is not likely to do so in man.

In *the light of recent knowledge of coronary* heart disease, it is clear that surgical procedures designed for the treatment of this disease should have certain clearly defined objectives and should be based on the known *physiologic and pathologic* facts.

Objectives of Surgery

1. To relieve precordial pain
2. To relieve right and left ventricular failure
3. To correct mechanical defects produced by myocardial ischemia
4. To increase exercise tolerance and ability to work
5. To prevent further loss of myocardial fibers
6. To prolong life expectancy

Each surgical procedure should be carefully scrutinized to judge whether it is capable of fulfilling the six objectives and is supported by adequate experimental and pathologic evidence.

Neurosurgery to Block Afferent Pain Pathways. INTERRUPTION OF CARDIAC PAIN FIBERS. The following procedures were designed to relieve precordial pain: cervicothoracic ganglionectomy, chemical nerve block, posterior rhizotomy, and pericoronary neurectomy.

When Jonnesco (1916) performed a trial *DI-5 sympathectomy for the relief of precordial* pain, there was little understanding of the mechanism or cause of this type of pain. There never was any question that the circulation in the myocardium would be improved, because it was not until 1928 that the mechanism of pain was clearly explained by Keefer and Resnick. *These authors* crystallized the concept that *precordial pain is due to a relative disproportion between myocardial demand for oxygen and its supply*

Neurosurgeons favor the neurosurgic treatment of precordial pain for the following reasons (1) the cutting of sensory nerves interrupts nerve pathways, (2) severance of motor acceleration nerves interrupts cardiopressor reflexes, (3) cutting of vasomotor nerves theoretically stops vasoconstrictor impulses to coronary arteries, thus permitting development of collateral circulation.

J. C White points out that "all cardiac pain *fibers function* from the upper three or at most four thoracic ganglia to reach the sensorium over the corresponding white rami communicantes, small nerves and their posterior nerve roots" These *fibers can be interrupted* by chemical injection of the four upper thoracic ganglia and their *rami* communicantes, resection of these ganglia without removal of the sympathetic chain, and interruption *of the upper four* posterior spinal nerve roots. The

results of these procedures are difficult to evaluate because the neurosurgical reports deal largely with pain, its relief, and neurosurgical techniques. Very little is mentioned in regard to the type of condition for which the patient is operated upon.

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Certainly the paravertebral injections of alcohol, as carried out by White, seem to be worthwhile in bed-rest patients with severe precordial pain.

Development of Collaterals, Anastomoses, or Both. The following procedures are used: ligation of cardiac vein, ligation of coronary sinus, bilateral ligation of internal thoracic artery.

Gross and Blum (1935) suggested that coronary sinus ligation would hasten the physiologic process of aging by the formation of collaterals. Both the procedures of great cardiac vein ligation and coronary sinus ligation in the treatment of coronary artery disease are based upon this concept.

Fauteux (1939–1940) reported a protective effect against anterior descending branch ligation after cardiac vein ligation, which persisted up to 1 year in animals; in 1946 he reported his results in 10 patients with precordial pain, 7 of whom had returned to work. Ripstein (1948) analyzed the results of 40 cases and reported that 72 per cent of the group had benefited from the procedure.

LIGATION OF CORONARY SINUS. Total ligation of the coronary sinus frequently causes marked venous congestion and turgidity of the ventricular wall. For this reason, Beck modified the operation by tying the coronary sinus at its entrance to the right atrium around a 3-mm probe. Beck is of the opinion that by this means, intercoronary collaterals are opened and a wider distribution of blood is brought about throughout the ventricular myocardium. In the past few years, he has performed this operation upon patients suffering from coronary artery insufficiency. The partial ligation of the coronary sinus is supplemented by abrasion of the epicardium and inner surface of the pericardium with a mechanical abrader and by the introduction of asbestos powder between the heart and the pericardial fat pads that are sutured directly to the heart muscle. This operation is

known as *the Beck I operation* and is now performed on patients with coronary artery disease in many centers, with reported good results.

BILATERAL LIGATION OF INTERNAL THORACIC ARTERIES. The rationale of the operation is based upon the known presence of capillary-sized anastomotic channels between the pericardiophrenic arteries and the coronary circulation through the pericardial fat pads and pericardial reflections over great vessels. This anastomotic bed is, as has been pointed out, entirely capillary in nature. According to the proponents of this operation (Battezzati et al., 1955), bilateral ligation of the internal thoracic arteries at the 2d interspace increases the rate of blood flow down the pericardiophrenic artery, thus causing blood to flow into the coronary artery bed.

A large series of patients operated upon by different European surgeons, particularly Italian, was reported in Turin, Italy, in which results have been stated to be excellent. However, in no instance has any one of these surgeons showed objective evidence that bilateral internal thoracic artery ligation opened up or developed extracardiac arteriolar-sized channels which communicated with the vessels of the myocardium. Although this operation is still being performed and reported in Europe, there is fundamentally no anatomic, physiologic, or experimental evidence to warrant its continued use in human beings. Some Russian surgeons have even combined the internal thoracic artery ligation operation with cardiopericardiopexy in the treatment of acute myocardial infarction. The results of this operation, as performed in North America and reported upon by surgeons from this continent, have not lived up to early expectations. Further, the North American workers, like the European surgeons, have not brought forth any evidence to show that the operation permits extracardiac channels of arteriolar or larger size to develop between the mediastinal vessels and the myocardium.

Myocardial Vascularization by Extracardiac Blood. Coronary artery narrowing, resulting in myocardial ischemia, usually occurs in the epicardial parts of the coronary vessels, leaving the arteriolar system lying within the myocardium comparatively intact. Surgical revascularization methods attempt to bypass points of coronary artery obstruction by connecting an extracardiac source of blood to the ventricular myocardium distal to these points of obstruction. Theoretically this is a sound concept, based upon the pathologic state that exists in human coronary artery disease. Practically, it has presented most difficult and perplexing problems, particularly in reference to (1) introduction of a volume of blood large enough to relieve myocardial ischemia, (2) equal distribution of the extracardiac blood throughout the myocardium, and (3) maintenance over months and years of the new extracardiac source of blood pathways.

SURFACE GRAFTS. Many types of tissue have been grafted to the surface of the left ventricle in the hope that these grafts would furnish the myocardium with a fresh extracardiac source of oxygenated blood.

Beck attached the left pectoralis major muscle to the surface of the left ventricle. This operation has been performed on animals, and on a few human beings, with *questionable results*. Many other types of surface grafts have also been employed.

O'Shaughnessy (1936–1937) brought a vascular flap of omentum up through the diaphragm and affixed it to the anterior surface of the left ventricle, where it formed anastomotic channels between the vessels of the omentum and the heart. Of 12 patients operated upon, 8 survived, 7 of the survivors continued to show increasing improvement. This operation has been performed twice by the author, without beneficial results but without mortality. One of the two patients had many gastrointestinal tract disturbances (*this apparently is one* of the complications experienced by O'Shaughnessy's patients). In addition, this operation has been criticized because of its combined abdominothoracic approach and because proper visualization of the pathologic changes in the heart cannot be achieved. It is no longer employed clinically.

Cardiopneumopexy. Lezius (1937) used the lower and middle lobes of the left lung and grafted them to the myocardial surface in animals. This method of myocardial revascularization was further explored by Carter et al.

Both Lezius and Carter demonstrated blood vessel channels between the pulmonary and coronary vessels, but information concerning the direction of blood flow, the volume of blood delivered through the new channels, and the duration is not available. This method has been criticized by Ghinst because it can deliver only unoxygenated blood; he further stated that the pulmonary vessels communicated with myocardial venous, not arterial, channels. Carter used this method in the treatment of coronary artery insufficiency in two patients, one of whom died, the other is said to have done well. Liebow et al modified this pro-

cedure by first ligating the arterial blood supply to the lingula; they then painted phenol on the mediastinal surface of the lingula and upon the ventricle before suturing the lingula to the surface of the left ventricle. In these experimental animals, they have produced evidence to indicate that the bronchial arteries to the lingula grow down the bronchus and eventually anastomose with the coronary vessels. This is an intriguing method of revascularization and may prove useful in the treatment of coronary artery disease in human beings.

Pericardial Fat Pad Grafts. In this operation, the medial diaphragmatic and phrenic fat pads are detached from the fibrous pericardium. The epicardium covering the surface of the myocardium is then removed by sharp dissection, and the fat pads are applied to the surface of the heart (Vineberg).

It has been shown by Vineberg et al and by Martineau that in the partially ischemic heart, arteriolar communication develops between the grafted pericardial fat pads and the coronary circulation Further, in one patient, 18 months after operation, retrograde injection of the circumflex artery showed the injection mass to enter the diaphragmatic fat pad Pericardial fat pad grafts, as a supplement to internal thoracic artery implant, have been used by the author since 1953 wherever possible

It may be that the major benefit derived from the Beck I operation is due to the introduction of extracardiac blood through the pericardial fat pads, which are applied to the surface of the heart after partial ligation of the coronary sinus, instrumental epicardial scraping, and irritation with asbestos powder

Skin Pedicle and Jejunum Grafts. Other surface grafts, which have been attempted in animals, include a skin pedicle flap, described by Moran et al (1952), and a jejunum graft, by Key et al (1954)

Key and coworkers report that in 75 per cent of their cases the jejunal pedicle vessels were open, while in 81 per cent there were anastomoses between the jejunum and the coronary vessels The type of anastomosis was almost entirely capillary, but they suggest that the amount of blood delivered through multiple capillary anastomoses would equal that produced by several small arteries Survival from anterior descending branch ligation was 93 1 per cent in grafted dogs, as compared with 28.7 per cent in control animals.

The jejunal graft is probably too major a procedure to be used in the treatment of human beings with coronary artery disease, since it involves, as does cardioomentopexy, an abdominothoracic approach.

ARTERIALIZATION OF THE CORONARY SINUS. Batson (1931) demonstrated that the heart can be kept alive and beating in an isolated state by perfusing it through the coronary venous system. This observation, corroborated by many workers, led to the idea, first described by Roberts et al. (1943), of anastomosing an artery to the coronary sinus, using the subclavian and brachiocephalic (or innominate) arteries.

Beck (1948) reported revascularization of the heart by grafting a systemic artery into the coronary sinus; he then modified it to a two-stage procedure known as *the Beck II operation*

In the first stage of this operation, anastomosis between the coronary sinus and the aorta is made by means of a jugular vein graft, and a ligature is placed around the coronary sinus just before its entrance into the right atrium Then, 3 to 6 weeks later, this ligature is partially closed at the second operation. Seven patients with coronary artery insufficiency were operated upon with a high mortality. Bailey modified the procedure and operated upon a comparatively large number of patients. He reports a total experience with 71 patients, 53 of whom had the Beck II operation, there were 8 deaths, and 8 blocked grafts were found at the second stage of the operation. The final results on these patients have not yet been published. Eighteen patients had Kralik's modification of Beck's procedure; again, the mortality and final results are not available.

The Beck II operation has been given up by Beck and by others because of its high mortality and because it was shown (Eckstein et al.) that retrograde perfusion of the coronary bed or through the graft lasts only for about 5 weeks; functional contact with the bed is then lost, probably because of obliterative venous change caused by high arterial pressure in the venous bed.

VENTRICULAR ARTERIALIZATION BY VASCULAR IMPLANTS. The implantation of a systemic artery into the left ventricular myocardium was first attempted by the author (1945).

The internal thoracic artery was detached from the chest wall between the 6th and 4th interspaces, it was divided between ligatures, and the proximal end was buried within a tunnel made in the myocardium. In its new location, the transplanted

vessel remains open because of side branches which are left open at the time of implantation and which bleed into vascular spaces surrounding the internal thoracic artery within the tunnel. The implanted vessel commences to bud at the end of 12 days, and, between 3 and 6 weeks, it sends out numerous arteriolar or larger branches which anastomose with the surrounding arteriolar network lying within the myocardium. When these thoracic-coronary anastomoses occur, which they do in 94 per cent of canine hearts made ischemic by ameroid constrictors placed on the coronary vessels, systemic arterial blood is propelled from the subclavian artery down the internal thoracic artery into the myocardial arteriolar network. There, it is distributed at first to the anterior portion of the myocardium and then, gradually, over a period of 5 months, as the ischemia progresses, to the entire left ventricle. Through these thoracic-coronary anastomoses, a rate of blood flow into the heart as high as 55 ml/min has been measured.

Sixty per cent of the arterial blood introduced through the internal thoracic artery 5, 6, and 7 months after implantation has been recovered from the coronary sinus, indicating that blood introduced through the implanted internal thoracic artery reaches the ventricular myocardial fibers.

It has been shown, both in animals and in man, that if there is myocardial ischemia, the implanted vessel, studied 6 months to 3 years after implantation, has remained patent and does not close off by intimal proliferation.

Many other workers obtained similar results with internal mammary artery implantation when the techniques outlined by the author were carefully followed. More recently, similar results have been obtained by Liebow, who implanted *the splenic artery* into the myocardium, and by Sabiston and Blalock, who have implanted *the carotid artery* in animals. Others, including the author, have used in animals the same principles to implant free homologous arterial grafts, which are attached at one end to the aorta Smith has substituted homologous grafts for nylon tubes, and has performed a nylon tube implant in human beings with coronary artery disease

The principle of internal mammary artery implantation is based upon two pathologic facts: (1) that coronary artery disease involves mainly the epicardial branches and, in particular, the first 3 to 4 cm of the origin of the main vessels; (2) that extensive intercoronary arteriolar anastomosis is present when myocardial ischemia develops because of coronary artery stenosis. Thus, the internal mammary artery, or any other vascular implant, bypasses the points of coronary artery obstruction to pour systemic extracardiac arterial blood into the ventricular myocardial arteriolar network. Once there, because of collateral arteriolar branches, the blood should reach all parts of the left ventricular myocardium.

Many hundreds of animals have undergone internal mammary artery implant, and well over 100 patients with coronary artery insufficiency have thus been treated The results have been most encouraging and will be discussed below.

Myocardial Circulation from Left Ventricular Lumen. The early, primitive reptilian creatures had no coronary arteries. The hag fish, which still swims in the South Pacific ocean, a 400-million-year-old prehistoric creature, has a systemic heart in which there are no coronary arteries and no nerve supply: the myocardium of the systemic heart receives nutrition through channels which communicate with the lumen of the ventricle. The mechanism of the myocardial circulation is that of ebb and flow, similar to a bathroom sponge being squeezed and relaxed. In our laboratory, we have been able to show that a beating heart in the animal can and will siphon Schlesinger mass from the left ventricular lumen when its two major coronary arteries are cut if it has had a previous epicardiectomy or an epicardiectomy plus the Vineberg sponge operation

Experience with patients undergoing the Vineberg sponge operation has disclosed that (1) the [illegible]

(3) these hearts enlarge These three facts suggested that the beating, ischemic left ventricle of the human heart, in the presence of occluded, or nearly occluded, coronary arteries can and does siphon blood from its own left ventricular cavity after removal of the epicardium [Fig 10-26(8)] These experimental and clinical observations become extremely interesting if an analysis is made of some of the operative procedures that have been used in the treatment of coronary artery insufficiency Thus, we find that in the Beck I operation, which has a good record of satisfactory results, the first stage is epicardiectomy, followed by partial ligation of the coronary sinus, and then by the application of pericardial fat pads to the left ventricular myocardium; before this is done, asbestos powder is sprinkled over the surface of the heart. The sprinkling of asbestos powder, in the author's belief, negates the value of the epicardiectomy. as

time goes on, scar tissue is formed, which prevents the myocardium from maintaining the loosened structure caused by epicardiectomy; thus, the numerous luminal myocardial vascular spaces, which were opened following *epicardiectomy*, tend to be *squeezed* closed again by the constricting scar tissue, which develops as the result of the use of asbestos powder. When epicardiectomy is performed, the heart enlarges *This enlargement* allows the *400-million-year-old* arterial luminal, luminal myocardial, and myocardial sinusoidal spaces to enlarge and to siphon blood into their spaces from the lumens of the left ventricle during diastole

When a sheet of Ivalon sponge is placed upon the bared left ventricular myocardium, this sheet tends to keep the myocardium in the same condition as it was at the time of application of the Ivalon sponge. It does not cause contraction, such as *that due to the application of asbestos or* talc, but rather maintains the status quo

Direct Attacks on the Coronary Arteries. CORONARY ENDARTERECTOMY. This procedure has been performed on a few patients. Unfortunately to date the mortality has been high and the end results have *not* been too satisfactory. However, with the introduction of better visualization of segmental coronary artery disease, the use of extracorporeal circulation, and hypothermia, it may be that this procedure will have its place in the *treatment* of coronary artery disease.

Endarterectomy combined with patch graft, as suggested by Senning, seems more promising than endarterectomy alone. It would seem to prevent reocclusion of the artery and offers a better chance for removal of the atheromatous material *from the artery and its penetrating* branches

Resection of segments—end-to-end anastomoses, with or without graft—has not been attempted on human beings This is still a laboratory procedure. The introduction of a systemic artery into the distal open end of a coronary artery is likewise a laboratory procedure but may be of value in the future

SELECTION OF OPERATIVE PROCEDURE

It is the author's belief that surgery of coronary artery disease, like surgery of a peptic ulcer, will make use of many methods and techniques Some years ago, surgeons argued as to the best technique for removing the stomach in the treatment of duodenal ulcer. Their medical confreres were arguing that surgery was of no use as a cure for peptic ulcer. Today there are few *who do not admit the value of* some *form of gastrectomy* in the treatment of intractable peptic ulcer. There is no further discussion as to what technique will be used, the surgeon has at his disposal numerous operative techniques and he tailors his operative procedure to suit the peculiarities of the case. Thus, it would seem that the selection of an operative procedure *for coronary artery disease* will depend upon the pathologic change that has occurred in the particular patient. For example, if, in the near future, it is shown in a young patient that the disease is segmental, very likely *endarterectomy* will be performed. If the disease is shown to be far advanced, with multiple lesions, *one of the bypass operations* will be used. Likewise, if the heart is in chronic failure, then it would seem that the *Vineberg sponge operation* or some modification of this operation, such as tapping *of the left ventricle*, may be used

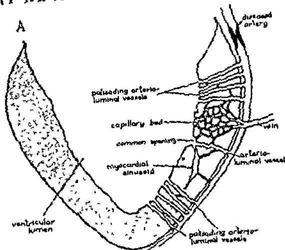


Fig. 10-26(8). Theoretical mechanism of endocardial nutrition in the ischemic heart after Ivalon sponge operation

However, whichever of these operations is chosen, it is the author's belief that proof should be shown that *surgical revascularization* has produced channels of arteriolar size between the coronary circulation and the extracardiac source of blood. These anastomotic channels should be large *enough to supply* the myocardium with as much blood as is *normally supplied by the left* coronary artery, and should be present for at least *6 months* or longer. The quantity of extracardiac blood de-

livered to the myocardium through the anastomotic channels should be sufficient to relieve myocardial ischemia at rest and under stress. The patient should survive without infarction after ligation of one or more major coronary vessels. Removal of the extracardiac source of blood after ligation of the anterior descending branch should result in death or infarction. Coronary artery sclerosis and occlusion should be produced and should be treated by the introduction of a fresh extracoronary source of blood. Blood flow measurements and oxygen-consumption studies should be made in order to determine the amount of blood and oxygen delivered to the heart. Anterior and circumflex coronary arteries should be gradually occluded as a means of producing left ventricular ischemia, and an evaluation of the revascularization procedure in the protection of the myocardium should be made under such conditions.

An operative procedure that experimentally fulfills the above criteria should theoretically be capable of attaining the following objectives, which, as pointed out earlier in this chapter, form the basic aim in treating coronary artery disease by surgical means (1) relief of precordial pain, (2) increase of exercise tolerance and ability to work, (3) prevention of further myocardial fiber loss, (4) prolongation of life expectancy, and (5) low operative mortality

A careful study of the various surgical procedures that have been outlined reveals that at present only three of them have extensive laboratory proof of value These are the Beck I, the Vineberg internal thoracic artery implantation, and the Vineberg sponge operations

SELECTION OF PATIENTS

In 1950 the author, like other surgeons in the field of coronary artery surgery, was given no opportunity to select patients Cardiac surgery, of any type, was considered highly experimental and extremely hazardous The only patients reporting for surgery were desperate, disabled, and pain-ridden persons, a large percentage of whom were bed-chair invalids Experience showed that the proper selection of patients for surgery should depend largely on the stage of development of the patient's disease, and the following criteria were agreed upon.

Indications for Surgery. PROVED CORONARY ARTERY DISEASE, WITH TYPICAL PRECORDIAL PAIN. The presence of proved coronary artery disease in itself is not sufficient indication for surgery unless the patient suffers from precordial pain which is truly causing difficulty. The author and his medical associates are firmly convinced that the occurrence of occasional precordial pain after unusual physical effort or excitement does not warrant a major surgical operation. Such a patient should be advised to forego the extra nine holes of golf. This point of view, however, is not subscribed to by Brofman and Beck, who believe that the presence of coronary artery disease in itself is an indication for surgery, even though the patient may be asymptomatic.

FAILURE TO IMPROVE ON MEDICAL TREATMENT OVER A PERIOD OF 1 TO 2 YEARS The question is: If one does not operate upon a patient with coronary artery disease who is asymptomatic, or who has occasional pain only, at what stage in his disease should surgery be performed? There is a great divergence of opinion on this point. The author's group, however, has elicited evidence that would seem to indicate *that operation should be performed on those patients who have failed to show improvement and whose pain causes disability after an adequate medical regime of 1 to 2 years' duration*

TWO CORONARY OCCLUSIONS WITH MYOCARDIAL INFARCTION. Patients who have had two or more coronary artery occlusions with infarction, even though they may be asymptomatic, have such a poor outlook for survival that some cardiologists are of the opinion that they should be accepted for surgery.

VENTRICULAR FAILURE, RIGHT AND LEFT, WITH OR WITHOUT PRECORDIAL PAIN.

Contraindications for Surgery. ASYMPTOMATIC CORONARY ARTERY DISEASE. As mentioned above, not all investigators consider this a contraindication.

RECENT INFARCTION, OR EVIDENCE OF DISEASE ACTIVITY Most cardiac surgeons and cardiologists are agreed that a period of 6 months should elapse after infarction before surgery is considered. This view, however, is not accepted by all. Smith operated, with what appeared to be a good result, on a patient who had had two recent myocardial infarctions.

MARKED ENLARGEMENT OF THE LEFT VENTRICLE The enlarged left ventricle may represent dilatation due to failure, hypertrophy due to myocardial ischemia, or a combination of both. In any of these cases, the Vineberg

sponge operation may be helpful. However, if the left ventricle is enlarged because of severe hypertension, it is questionable, because of numerous diseased arterioles within the myocardium, whether the patient should undergo any form of revascularization surgery.

RAPID PROGRESSIVE DETERIORATION. Many surgeons prefer to wait for some degree of stabilization in these patients. Not infrequently, the augmentation of precordial pain may be a precursor of coronary artery thrombosis and infarction. Such patients may die in the anesthesia room, on the operating table, or shortly thereafter, from an exacerbation of their disease.

MALIGNANT HYPERTENSION, SEVERE DIABETES, OR OTHER INCURABLE DISEASES

THE "ANGINA DECUBITUS" GROUP. This group consists of patients who suffer pain at rest without exciting cause. Patients who experience night pain or pain at rest while watching television or after eating, do not necessarily have angina decubitus. Patients with true angina decubitus should not undergo revascularization surgery, the mortality is high and the end results are poor in those who survive operation. Pathologic examination of the hearts of patients who have died from angina decubitus reveals that such patients generally were living with one pin-point opening, or perhaps two, in their major coronary arteries. There is insufficient coronary circulation to carry such patients through anesthesia without left ventricular failure, ventricular fibrillation, or a fresh coronary thrombosis within 3 weeks of surgery. Further examination of such hearts shows that, because of the prolonged period of ischemia, which in the author's series was well over 10 years, there is little myocardial muscle fiber left to revascularize.

The view that surgery is contraindicated for patients with angina decubitus has been queried by some, who are unwilling to suggest surgery to patients with less advanced disease, still able to get along with an occasional nitroglycerin tablet. This is similar to suggesting that a patient with mitral stenosis who is doing well on digitalis does not require mitral commissurotomy. Unquestionably such patients do well for a while without commissurotomy, but it is well known that the death and complication rate of patients with mitral stenosis mounts steadily with each succeeding year that surgery is postponed. The same is true of coronary heart disease. The longer the disease process is active, the greater the danger for the patient.

The recent report of White et al. on a 25-year follow-up of patients with myocardial infarction can be used as a guide in the selection of patients for revascularization surgery. To quote these authors, "The best aid to long term progress following myocardial infarction is the degree of recovery of the patients following the acute period of illness." In their patients who had complete medical recovery following infarction, 82 per cent were alive at the end of 5 years, whereas of the entire group of 162, only 49 per cent were alive 5 years after myocardial infarction.

Although patients with precordial pain without infarction appear to have a better future, White states that the mortality in patients with coronary disease who have pain is usually 7 per cent above the expected mortality. The asymptomatic patient, therefore, has a better prognosis, the hearts of such patients being well taken care of by their undiseased "good-neighbor" arteries, which are known to send collaterals to the ischemic zone, so that there is no need for extracardiac sources of blood. Any type of revascularization surgery upon such patients can do no more than nature has already done.

PREOPERATIVE INVESTIGATION AND POSTOPERATIVE CARE

Diagnosis. Preoperative investigation is absolutely essential, in order to establish a firm diagnosis and to ascertain the presence or absence of other disease or condition that might be the source of the patient's symptoms.

In general, chest pain that is not initiated by physical activity or emotion and does not disappear rapidly with rest should be regarded with suspicion. Generally, a pain of long duration that is not made worse by exercise and is not relieved by nitroglycerin, is not caused by myocardial ischemia. A search for hiatus hernia, biliary tract disease, peptic ulcer, and even cervical or upper thoracic disks may disclose the source of the pain. The ECG is of value when it is positive. Failure to obtain electrocardiographic evidence of coronary artery disease with the Master's two-step test or the treadmill exercise may leave the diagnosis in doubt.

Roentgenology. During the past few years, it has become possible to outline the coronary arterial tree. It is the author's opinion that in all patients being considered for surgical treatment of coronary artery insufficiency, the degree and location of occlusion of the coronary arterial tree should be outlined by one of the numerous techniques now available. Only by *coronary arteriography* is it possible to decide whether the patient has any coronary artery disease. Frequently in the author's clinic, patients have had clinical histories strongly suggesting that they were suffering from coronary artery insufficiency; yet the coronary arteriogram has failed to show any evidence of disease. Such patients have not undergone any form of surgery.

It is the author's belief that if one coronary artery is narrowed but two major coronary arteries are free of disease, the patient will probably develop intercoronary collaterals, which will bring blood from the normal coronary arteries into the area supplied by the narrowed diseased vessel. If such a patient fails to improve clinically, one should resort to operation not only to introduce extra blood but also to cause a good distribution of the blood that has been introduced through the two good coronary arteries

If two major coronary arteries have been narrowed to an average cross-sectional area of 50 per cent or more of their combined luminal areas, a point of critical narrowing has been reached, and the patient, in the author's opinion, is in danger of ventricular fibrillation or myocardial infarction Such patients should undergo surgical intervention, and the operation must be designed to suit the particular condition in the individual heart under consideration

Blood Pressure. Blood pressure should be taken four times daily and once at night, so that an average blood pressure level may be established.

Fluid Balance. Preoperative daily intake and output measurements when averaged form a sound base line for the amount of postoperative fluid to be administered.

Operative Care. The patient with coronary disease is usually apprehensive. For this reason, care should be taken to see that he is under deep sedation and is not taken to the operating room until the anesthetist is ready to start the anesthesia. Substernal pain prior to operation, when not relieved by nitroglycerin, may reflect a new occlusion with infarction and is a contraindication to surgery. Such patients should be returned to bed and watched for at least 1 week. The surgeon should ask the patient in the anesthesia room if he has precordial pain, if such pain is present, the operation should be postponed During the induction of anesthesia and the operation, the blood pressure must be maintained with Neosynephrine drip, which may be administered through a cut in the foot or arm. To avoid excess fluid, the Neosynephrine solution is strengthened as needed, starting with 5 ml Neosynephrine per 500 ml of 5 per cent glucose and water. It is advisable to insert a Wangensteen tube into the patient's stomach after induction of anesthesia to prevent gastric pressure on the heart postoperatively and to prevent paralytic ileus, which sometimes develops postoperatively.

Postoperative Care. The most important factor in postoperative care is to maintain the blood pressure at average preoperative levels Failure to do so favors cerebral and coronary thromboses.

Early ambulation is encouraged after certain types of operation, but after the internal mammary artery implant procedure, in which the pericardium is left open, movement is not permitted for 48 hr. After any coronary surgery, the patient has to live upon his own inadequate coronary circulation until extracardiac sources of blood can reach the myocardium. He should therefore be treated as though he had had a coronary artery occlusion with infarction, and should be given 4 to 6 months of convalescence to permit the new vessels to grow large enough to be of real value

Anticoagulant Therapy. The author and his coworkers have used anticoagulant therapy, by oral administration, starting on the second or third postoperative day. The value of this therapy in the treatment of coronary artery disease may be questioned, but it may be helpful in preventing thrombosis initiated by operation and bed rest.

RESULTS

The treatment of coronary artery disease is probably one of the most difficult to evaluate because of the numerous and unpredictable variations that occur during the natural course of the disease This is true for both medical and surgical therapy The comparison of individual cases is difficult, it is not so difficult, however, to compare groups of cases that fit into a certain broad classification. Such a basic classification has been established, and with excellent effect, for the surgery of mitral stenosis.

In the author's experience, there are two main groups of patients in which entirely dif-

ferent results may be expected from revascularization surgery. These are (1) patients with angina decubitus (i.e., pain at rest without exciting cause), and (2) patients with no pain at rest. Until objective radiologic evidence of improved myocardial circulation after surgery is available, the observer must rely upon the following criteria as indications of improvement: (1) survival, (2) disappearance of precordial pain for more than 6 months, (3) increase in work and exercise tolerance, (4) improvement in the ECG, and (5) failure to develop fresh infarction.

Survival. This pertains to both postoperative and long-term survival. The American College of Surgeons has defined the period of postoperative survival as the 30 days immediately after the operation. *Death during this period, no matter from what cause, must be recorded as a postoperative death.*

Dana and Ohler found a 7 per cent mortality of cardiac origin in patients who had suffered from pain at the time major surgery was performed. The same authors point out that there was no mortality of cardiac origin in patients with previous myocardial infarction who were asymptomatic at the time of major surgery, whereas the mortality was 40 per cent in a small group of patients who had had recent infarctions. Patients with coronary

tality above this figure fundamentally represents the true operative mortality for any given procedure.

Disappearance of Precordial Pain. Pain is subjective and thus very difficult to estimate both before and after operation. For this reason, the author's patients are seen by two cardiologists and a psychiatrist. Certainly, the disappearance of pain a few days or even a few weeks after surgical revascularization may be a psychologic phenomenon. The experience of the author's group indicates that *an attempt to evaluate the effect of an operative procedure should not be made less than 6 months after the operation.*

Increase in Work and Exercise Tolerance. In order to measure the improvement after operation, a careful record is made of the patient's ability to work and exercise before operation. Accurate questioning gives some indication of his ability as to exercise, e.g., the question, "How far can you walk in your town at the same pace as the crowd on the street?" invariably brings out that the patient may be able to walk a half-mile or so, but at a very reduced pace. The Master's two-step test and the treadmill, however, permit a much more dependable estimate of the patient's ability to exercise.

Improvement in the Electrocardiogram. The results obtained by electrocardiographic studies leave much to be desired. In the author's laboratory, the ECG has frequently failed to show evidence of improvement when the animal's exercise tolerance has returned to normal and when, later, autopsy findings have proved satisfactory myocardial vascularization. One should not place too much reliance on the ECG in estimating postoperative improvement or lack of it.

Failure to Develop Fresh Infarction. Revascularization surgery does not alter the predetermined course of coronary artery disease except to prevent myocardial fiber loss. Thus, coronary artery occlusion may and does sometimes occur after a revascularization procedure.

Evidence is now accumulating to indicate that *coronary artery occlusion may occur without evidence of myocardial infarction following a satisfactory revascularization.* This appears to have been true in at least five cases in which internal mammary artery implantation was performed.

There are three operations in use in the treatment of coronary artery disease in human beings which have had a most extensive experimental background and a long period of clinical trial. They are (1) the Beck I operation; (2) the internal mammary artery implantation (Vineberg); and (3) the Vineberg sponge operation.

The Beck I operation has a low over-all mortality; the good results are most impressive. Brofman reports 400 patients operated upon with an operative mortality of 5 per cent and a late mortality of 15 per cent. One hundred and ten of these patients were followed 3 to 5 years; the results were as follows:

Condition	*Percentage*
Excellent (little or no pain, working full time, no subsequent heart attacks)	39
Good (occasional heart symptoms, working more than before operation)	31
Fair (little apparent improvement)	6.4
Poor (no apparent benefit)	1.8
Died during operation	5
Died later	15
Total	98.2

It should be noted that of the 110 patients, 45 had severe precordial pain, 45 had moderate pain, and only 20 showed mild symptoms before opera-

Roentgenology. During the past few years, it has become possible to outline the coronary arterial tree. It is the author's opinion that in all patients being considered for surgical treatment of coronary artery insufficiency, the degree and location of occlusion of the coronary arterial tree should be outlined by one of the numerous techniques now available. Only by *coronary arteriography* is it possible to decide whether the patient has any coronary artery disease. Frequently in the author's clinic, patients have had clinical histories strongly suggesting that they were suffering from coronary artery insufficiency; yet the coronary arteriogram has failed to show any evidence of disease. Such patients have not undergone any form of surgery.

It is the author's belief that if one coronary artery is narrowed but two major coronary arteries are free of disease, the patient will probably develop intercoronary collaterals, which will bring blood from the normal coronary arteries into the area supplied by the narrowed diseased vessel. If such a patient fails to improve clinically, one should resort to operation not only to introduce extra blood but also to cause a good distribution of the blood that has been introduced through the two good coronary arteries

If two major coronary arteries have been narrowed to an average cross-sectional area of 50 per cent or more of their combined luminal areas, a point of critical narrowing has been reached, and the patient, in the author's opinion, is in danger of ventricular fibrillation or myocardial infarction. Such patients should undergo surgical intervention, and the operation must be designed to suit the particular condition in the individual heart under consideration.

Blood Pressure. Blood pressure should be taken four times daily and once at night, so that an average blood pressure level may be established

Fluid Balance. Preoperative daily intake and output measurements when averaged form a sound base line for the amount of postoperative fluid to be administered.

Operative Care. The patient with coronary disease is usually apprehensive. For this reason, care should be taken to see that he is under deep sedation and is not taken to the operating room until the anesthetist is ready to start the anesthesia. Substernal pain prior to operation, when not relieved by nitroglycerin, may reflect a new occlusion with infarction and is a contraindication to surgery. Such patients should be returned to bed and watched for at least 1 week The surgeon should ask the patient in the anesthesia room if he has precordial pain, if such pain is present, the operation should be postponed. During the induction of anesthesia and the operation, the blood pressure must be maintained with Neosynephrine drip, which may be administered through a cut in the foot or arm. To avoid excess fluid, the Neosynephrine solution is strengthened as needed, starting with 5 ml Neosynephrine per 500 ml of 5 per cent glucose and water It is advisable to insert a Wangensteen tube into the patient's stomach after induction of anesthesia to prevent gastric pressure on the heart postoperatively and to prevent paralytic ileus, which sometimes develops postoperatively.

Postoperative Care. The most important factor in postoperative care is to maintain the blood pressure at average preoperative levels Failure to do so favors cerebral and coronary thromboses

Early ambulation is encouraged after certain types of operation, but after the internal mammary artery implant procedure, in which the pericardium is left open, movement is not permitted for 48 hr After any coronary surgery, the patient has to live upon his own inadequate coronary circulation until extracardiac sources of blood can reach the myocardium He should therefore be treated as though he had had a coronary artery occlusion with infarction, and should be given 4 to 6 months of convalescence to permit the new vessels to grow large enough to be of real value.

Anticoagulant Therapy. The author and his coworkers have used anticoagulant therapy, by oral administration, starting on the second or third postoperative day. The value of this therapy in the treatment of coronary artery disease may be questioned, but it may be helpful in preventing thrombosis initiated by operation and bed rest.

RESULTS

The treatment of coronary artery disease is probably one of the most difficult to evaluate because of the numerous and unpredictable variations that occur during the natural course of the disease. This is true for both medical and surgical therapy The comparison of individual cases is difficult; it is not so difficult, however, to compare groups of cases that fit into a certain broad classification. Such a basic classification has been established, and with excellent effect, for the surgery of mitral stenosis

In the author's experience, there are two main groups of patients in which entirely dif-

it to a femoral artery. Two of the 3 patients survived the procedure, 1 of them died 10 days later from a fresh coronary artery occlusion and infarction

There is considerable disagreement at present as to the best means of bringing about circulatory assistance in cases of coronary artery shock. Some subscribe to the principle outlined by Dennis and his group, who indicated that a good result can be obtained by using the pump-oxygenator Others feel that this technique hinders rather than helps the failing heart; this opinion, however, has been based on experience in the experimental laboratory, which is not comparable with experience in human beings, where there is failing circulation because of a failing left ventricle.

Some investigators have suggested that circulatory assistance in coronary artery shock be provided by passing a catheter through the superior vena cava into the left atrium through the interatrial septum, thus withdrawing the blood from the left atrium and passing it into a heart-lung machine and back into a femoral artery. *Left heart bypass* is suggested to relieve the left heart of any strain. This procedure has been carried out, to the author's knowledge, in one patient in Sweden, but unfortunately the patient died. The future of circulatory assistance in coronary shock is certain to be great.

tion. The patients who died later had an average preoperative duration of symptoms of 4 years. Forty per cent of the patients had two or more episodes of acute myocardial infarction before operation Brofman reports that 20 per cent of the patients had left ventricular enlargement but only a few had evidence of any congestive failure.

Hill has surveyed the results of the first consecutive 36 patients who underwent internal mammary artery implantation at the Royal Victoria Hospital Figures have been compiled by Hill on the basis of a 5- to 9-year follow-up. The operative mortality for this group was 13 per cent, on the basis of the author's experience, 4 of the 5 patients who died in this series would not be operated upon today. The 5- to 9-year study of the 31 patients who survived the operation showed marked improvement in 67 7 per cent of them. In this group, 7 per cent had complete pain relief within the first 9 months As time passed, an increasing number of patients became pain-free, until at the end of 3 years 37 per cent of the group were completely free of pain. Some 75 per cent of these patients had been disabled before surgery, 72 per cent returned to work after surgery *The combined Vineberg and Walker series of 110 patients with coronary artery disease treated by internal mammary artery implantation showed that the over-all mortality rate for the two series for patients who had had no pain at rest was 5 8 per cent.*

In the group of 110 patients in which there was no precordial pain at rest, 72 per cent were totally disabled prior to operation. Most of the patients could walk approximately one-half a city block prior to operation. After the operation, over 78 per cent had no pain or had less pain, and 79 per cent returned to work.

The Vineberg Sponge. This operation has been used in the past 3 years with considerable success in the treatment of patients over 60 years of age, those with ventricular hypertrophy and those with chronic left and right ventricular failure. The internal mammary artery implantation and the Beck I operation have been reserved for patients with no precordial pain at rest without exciting cause and with small left ventricles.

Patients with chronic ventricular failure who had been digitalized and "dried up" before operation, in general withstood surgery quite well, the operative mortality for a group of 24 patients was less than 8 per cent In the entire group, 22 individuals had had previous infarction and 21 had chronic ventricular failure (right, left, or both). Twenty-nine patients were suffering from precordial pain, and 19 were unable to work. Following surgery, 15 patients were pain-free and 18 improved markedly.

SURGERY OF LESIONS OF THE HEART RESULTING FROM CORONARY ARTERY INSUFFICIENCY

In the operating room, the author has encountered two unsuspected cases of *right ventricular aneurysm*. Both cases were treated by the Ivalon sponge procedure. There are, however, in the literature, reports of *left ventricular aneurysms* that have been successfully treated using extracorporeal circulation, by resection of the aneurysm and resuturing of the cut surfaces of the left ventricle.

When the aneurysm is saccular, the incision is small, when the aneurysm is large and fusiform, a very large portion of the ventricle has to be resected and usually a considerable quantity of intraventricular thrombus must be removed Usually patients with this condition come to the attention of the surgeon following two to three previous infarctions and because of left ventricular failure Recently, the author resected a left ventricular aneurysm which involved the entire anterior surface and a good part of the lateral surface of the left ventricle The incision measured over 20 cm in length The patient was in chronic left ventricular failure following three myocardial infarctions The aneurysm extended out to the chest wall in the midaxillary line. Resection was carried out without difficulty, using extracorporeal circulation, and the patient had an uneventful postoperative convalescence

The *ruptured intraventricular* septum following myocardial infarction has likewise been repaired with success in a few instances using extracorporeal circulation. Some of the patients have died later from another attack of myocardial infarction, but at autopsy, the repaired intraventricular septum has been shown to be unchanged.

Ruptured papillary muscles usually occur because of rupture of a lateral papillary muscle which results in mitral insufficiency. A few patients with this condition have been operated upon, and the mitral insufficiency has been di-

re[illegible]

ni[illegible]

a word concerning circulatory assistance in the treatment of *coronary artery shock*. The usefulness of circulatory assistance in the treatment of coronary artery shock was first reported by Dennis, who used a pump-oxygenator, removing blood from a femoral vein and returning

10

The surgery of ventricular aneurysms

HOUCK E. BOLTON AND CHARLES P. BAILEY

An aneurysm of the ventricle of the heart may be defined as a more or less localized outpouching of the continuity of the wall of the ventricular chamber. Such aneurysms may be the result of a congenital malformation (so-called diverticulum), accidental or surgical trauma, or degenerative changes in the muscle fibers (postinfarctional).

The first recorded case of ventricular aneurysm was reported by Hunter (1757). The first operative attack upon such a lesion was made inadvertently by Sauerbruch (1937). While attempting to remove a mediastinal tumor, he made a limited incision into such an aneurysmal sac, allowing palpation of the interior of the ventricular chamber. This cardiotomy incision was closed by simple suturing of the opening.

Deliberate suture plication and constriction of the base of an aneurysm sac in order to decrease the size of the lesion was described by Beck (1944). More recently, D'Allaines reported a case in which a similar principle was employed. Actual resection of a ventricular aneurysm was first attempted by Glover (1953). Using a somewhat different technique, Bailey (1954) performed a subtotal resection of a postinfarctional type aneurysm with survival. Since that time, eight additional patients have been treated similarly with but one death.

ETIOLOGY

The development of a *diverticulum of the ventricle* is believed by Drennan and Van de ... s of ... The ... any unusual increase in intraventricular pressure occur during prenatal development.

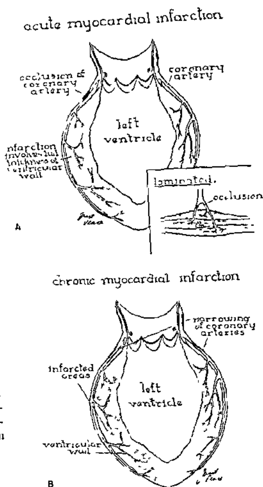


Fig. 10-27 A. Acute myocardial infarction involving full thickness of ventricular wall is shown in comparison to the laminated type of acute myocardial infarction which involves a layer of muscle in the myocardial wall. B. Chronic myocardial infarction demonstrating spotty irregular areas of myocardial fiber death and replacement by scar tissue.

tion and, to a degree, impedes filling from the left atrium—similar to the dysfunction associated with aortic regurgitation

DIAGNOSIS

Patient Selection. The symptoms, signs, and electrocardiographic changes associated with ventricular aneurysms may provide only a suspicion of its presence. An abnormal bulge in the x-ray silhouette and a paradoxically pulsating mass seen along the heart border by fluoroscopic examination are observed in most cases (Fig 10-28A) Those patients having an actual paradoxic movement of the wall or having signs of chronic heart failure following a history of myocardial infarction should be studied by roentgen- or electrokymography or, preferably, by opacification of the ventricular chamber. Such opacification by a contrast medium, such as 70 per cent Diodrast or 90 per cent Hypaque, is now done by direct ventricular puncture in preference to left atrial injection. Serial radiographs demonstrate the changes in size with systole and diastole and confirm the site of origin from the ventricular chamber (Fig. 10-28B, C).

Nonvisualization of the lumen of an attached aneurysm by such a method of examination may suggest that the sac contains soft thrombotic material. Paradoxic motion is not observed in these cases. Anticoagulant therapy to preclude embolization may be used in such a case in preference to surgical methods. If treated medically, anticoagulant therapy

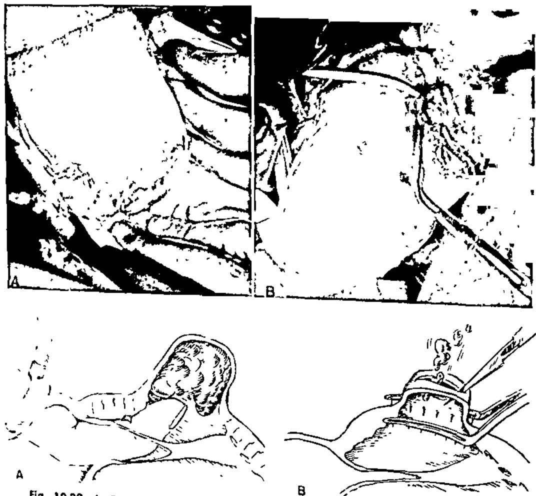


Fig 10-29. A Diagram demonstrates digital exploration of the aneurysm through the appendage and mitral valve The photograph shows the intact aneurysm. B. The diagram shows the method of "flushing out" contained thrombi, prior to closing the clamp. The photograph shows the clamp applied to the base of the aneurysm.

Posttraumatic aneurysms will undoubtedly become more common. The advent of cardiac surgery has introduced the necessity of many ventriculotomies, and one must assume that a very small percentage of such procedures will be followed by a weakened area of the myocardium. Other types of accidental injuries likewise provide a possible source of aneurysmal lesions.

The most common cause of ventricular aneurysm is the myomalacia which follows *acute coronary arterial occlusion*. On the basis of Master's estimated incidence of myocardial infarction, it is believed that between 25,000 and 200,000 new cases of ventricular aneurysm develop annually in the United States alone. These aneurysms, unfortunately, are frequently overlooked.

PATHOPHYSIOLOGY

As the entire thickness of the myocardium is involved in large infarcts, most of the muscle fibers are destroyed and undergo liquefaction necrosis The central portion of the infarct heals much more slowly than does the periphery. Should undue strain be placed upon this area during the healing phase, the thin central portion may bulge outward into a noncontractile paradoxically expansile pouch Since the aneurysm develops initially from a large area of myomalacia, it becomes sessile with no true neck. The overlying pericardium becomes adherent and markedly thickened, thereby preventing rupture after the initial healing has begun.

An aneurysm exerts an extremely deleterious effect upon the ability of the ventricle to maintain an adequate net stroke output. Because of its semielastic nature, the wall of the sac stretches during systolic contraction of the ventricle, producing a paradoxic pulsation during systole. The dysfunction produced is similar to that present in mitral regurgitation. A certain portion of the ventricular content is wasted since it is not expelled into the aorta During diastole, the sac collapses, emptying its contained blood into the chamber of the ventricle This produces left ventricular dilata-



Fig. 10-28. A. Posteroanterior and lateral roentgenogram in a 42-year-old white male showing a true ventricular aneurysm with a small neck. B Contrast visualization by direct injection of 70 per cent Diodrast into the left ventricle C. Postoperative contrast visualization roentgenogram showing an essentially normal cardiac chamber.

tained thrombi is provided by wide incision of the aneurysm. Hemostasis is restored promptly by the application of a special clamp designed to prevent slippage from the neck of the sac (Fig. 10-29B). Postoperative embolization may be prevented by anticoagulant therapy.

SURGICAL TECHNIQUE

Although Beck advocated reduction in size of these aneurysms by reenforcement with fascia lata, this type of procedure would seem to be inadequate and perhaps hazardous in the presence of intraluminal thrombosis. Complete excision of the sac, as undertaken by a number of surgeons, has been followed by a fatal outcome in some cases These deaths have been attributed to embolic episodes or to the persistence of intractable heart failure following the surgery. Experimental work suggests that reduction in the diastolic capacity of the underlying ventricular chamber may precipitate chronic heart failure The type of circulatory obstruction produced by ventricular resection in dogs appears similar, functionally, to that which is observed in experimentally produced mitral stenosis. Postoperative compensatory dilatation of the ventricle was not observed in the authors' experience

The currently employed method of ventriculoplasty avoids both the threat of embolic episodes and the chronic heart failure because of a wide resection with reduction in left ventricular filling capacity The aneurysmal sac is "tailored," so that expansion is prevented and so that the heart is changed to one of optimum shape and efficiency. The thin apical portion of the sac is resected, while the strong basal portion is utilized to construct a secure fibrous wall of the ventricle (Fig 10-30) If a papillary muscle takes origin from the wall of the sac, it may be included in the clamp and suture line The normal valvular supports will remain unchanged, and mitral incompetence will not be created

A special multitoothed clamp is applied across the base of the sac immediately after the fundus of the aneurysm is opened. This allows the intraventricular pressure to eject any thrombotic material before the clamp is closed completely. This precaution has seemed to prevent systemic embolization.

TABLE 10-2. RESULTS OF OPERATION

Type of aneurysm	*No of cases*	*No. of deaths*	*Cause of death*
Congenital	1	0	0
Posttraumatic	2	0	0
Degenerative	6	1	Systemic embolization

The surgical problem is significantly altered in false aneurysms following trauma or surgical incisions The actual size of the left ventricular chamber may remain unaltered, and the ventricle most frequently communicates with the aneurysm through a small fistula. Excision of the sac with suture repair of the communicating opening has provided a permanent correction.

The results of excision in congenital diverticula have been excellent The cases discussed include one such patient. Excision was accomplished by clamping the base of the sac and by simple suture. However, in the treatment of the postinfarctional aneurysm, results have been generally less satisfactory. Using the tailoring principle of ventriculoplasty, five patients have survived The death reported in this group was due to dislodgment of an attached mural thrombus with systemic arterial embolization This accident may be avoided by the "flush-out" technique as described above. The remaining patients in this group have attained an excellent postoperative result, with the exception of one patient who developed a second aneurysm.

The posttraumatic aneurysms encountered followed previous heart surgery One of them occurred through the weakened cicatrix at the site of a ventricular tear produced during mitral commissurotomy The other occurred through a ventricular scar due to transventricular aortic commissurotomy These aneurysms were treated by simple suture of the defect in the ventricular wall, with a good postoperative result in each case.

should be planned for the patient's entire life span, or until such a time when the aneurysm and its contained clot may be eradicated.

Since most of these patients present a history of one or more myocardial infarctions, it must be assumed that some degree of damage exists even in the remaining "normally functioning" myocardium. These patients are poor surgical risks. Surgical intervention should be deferred until 6 months after the last coronary occlusion. This period of healing will provide adequate time in which dense scarring may be formed about the neck of the aneurysmal sac. Excision should be recommended only when paradoxic motion can be demonstrated by kymography, fluoroscopy, or ventricular opacification. This is substantiated by a review of postmortem studies of aneurysms. Rupture of a postinfarctional aneurysm seldom occurs. The mechanism producing death is usually congestive failure—related to the mechanical inefficiency produced by the presence of the semielastic sac. More infrequently, contained thrombotic material may become detached and result in peripheral embolization.

During the surgical procedure, certain steps are essential to prevent systemic embolization. Intracardiac exploration by way of the left auricle and the mitral valve provides an accurate method for the recognition of mural thrombi about the neck of the sac (Fig. 10-29A). Complete external flushing of con-

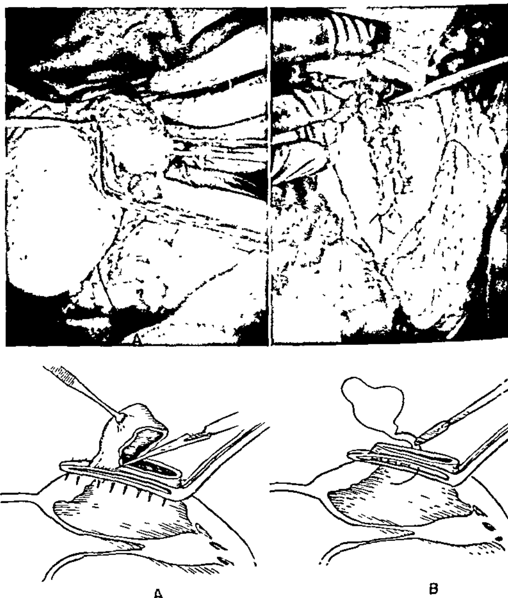


Fig. 10-30. A. The diagram and photograph show the actual excision of the redundant aneurysmal wall. B. The diagram demonstrates the first line of sutures being placed through the clamp's fenestration. The photograph shows the completed suture line after removal of the clamp.

PART II

Disturbances of the heart rate and rhythm; excitability and conduction disturbances

PART II

Disturbances of the heart rate and rhythm; excitability and conduction disturbances

1

Disturbances due to modified function of the sinoatrial node

ALDO A. LUISADA

SINUS TACHYCARDIA

Cause and Types. The most common sinus tachycardia is caused by *exercise*. It lasts for a long time if the heart muscle is weak.

Digestion is often accompanied by increased heart rate. This occurs if the quantity of food and drink is too great or if the heart muscle is weak. The ingested fluid increases the volume of circulating blood, thus increasing cardiac strain.

Assuming the erect position is accompanied by an increased heart rate because of decreased intensity of carotid sinus reflexes. *Emotion* is accompanied by tachycardia. Many *drugs* and *poisons* also cause tachycardia. Among them, caffeine and nicotine are the most commonly used. *Fever* is usually accompanied by rapid heart action.

Endocrine disorders may be accompanied by rapid heart, the most frequent such cause being hyperthyroidism.

Valvular defects, pericardial lesions, and *high or low blood pressure* may be accompanied by sinus tachycardia, because they either increase the work of the heart and, therefore, are the equivalent of exertion, or cause reflex acceleration of the heart beat through changes of stretch of vascular receptors.

If the *myocardium is weak*, the heart maintains its output by reducing systolic discharge and increasing its rate.

Sympathetic irritation or a *lesion of the vagus nerve* may be responsible for a rapid pulse.

Signs and Symptoms. The patient usually does not feel the tachycardia, but if it is too high, he may complain of *palpitation*.

The pulse is regular and often small. It has no fixed rate; therefore, exercise, change of position, and respiration may vary it. Spontaneous variations are also common. The heart *sounds* are regular and frequently have equal duration and loudness.

Graphic Methods. ELECTROCARDIOGRAM. The atrial and ventricular waves follow each other in a normal way (Fig. 11-1A). The P-R interval may be slightly longer than normal but is not over 0.20 sec. Diastole is short, so that the end of the T wave is near the following P wave. In the adult, the rate varies between 90 and 150 but is seldom above 100. Occasionally, higher figures have been described.

JUGULAR TRACING. There may be fusion of the *V* wave with the following *A* wave.

PHONOCARDIOGRAM. The heart sounds are short and loud. A triple rhythm is not unusual because of tumultuous ventricular filling.

Diagnosis. Sinus tachycardia can usually be recognized because (1) it is connected with a definite cause; (2) it does not start suddenly; (3) it is well tolerated; (4) very seldom does the rate exceed 150; (5) the rate frequently changes; and (6) there is a normal electrocardiogram.

Paroxysmal tachycardia gives an abnormal electrocardiogram, starts suddenly, and is less well tolerated.

Treatment. Treatment is directed, whenever possible, to removal of the cause. Whenever high excitability of the sympathetic system is involved, *ergotamine* or *Hydergine* may be used.

Digitalis or *quinidine* is indicated in some cases. *Coramine* may be used with low blood pressure.

Rest, sedatives, and treatment of the thyroid condition are necessary in some cases. In particularly severe and intractable cases, removal of the upper thoracic sympathetic ganglia (second to fifth) may be necessary.

SINUS BRADYCARDIA

Cause and Mechanism. Sinus bradycardia may result from *poisoning* or *infection*. Poisoning from biliary salts (jaundice) or products of metabolism (uremia) is not uncommon Poisonous mushrooms, morphine, and digitalis cause bradycardia. Typhoid, diphtheria, rheumatic disease, mumps, pneumonia, and cholera may cause relative or absolute sinus bradycardia. In particular, rheumatic carditis causes bradycardia in about 10 per cent of the cases.

Convalescence is frequently accompanied by a slow pulse due to sinus bradycardia.

Increased intracranial pressure is revealed by a slow pulse *Visceral colicky pain* also is usually accompanied by slow pulse.

Patients with *myocardial fibrosis* may have a persistently slow pulse which is only slightly affected by the position of the patient.

Hypothyroidism is frequently associated with bradycardia, which may even reach the low rate of 40 per minute.

Patients with *abnormal sensitivity of the carotid sinus* have a sudden slowing of the pulse when a change of position or an external compression stimulates the carotid receptors.

Lastly, some *normal individuals* have a constantly slow pulse, their condition has been called *vagotonia*. *Athletes* frequently have a slow pulse.

In all these cases, three possible mechanisms may exist. (1) a continuous reflex action slows down the heart by way of the vagus nerve, (2) there is a high tonus and excitability of the medullary center of the vagus, so that normal stimuli are sufficient for maintaining the slow pulse; (3) the SA node itself is affected.

The reflex mechanism is involved in the cases with visceral pain or hypersensitive carotid sinus and may be involved in cases of myocarditis. A high excitability of the vagus occurs in patients with high intracranial pressure, in hypothyroidism, in drug action, and in normal individuals with slow pulse. Direct change of the function of the SA node is involved in myocardial fibrosis, in severe myocarditis, and also in cases of poisoning. However, in many cases, a double mechanism (action on the

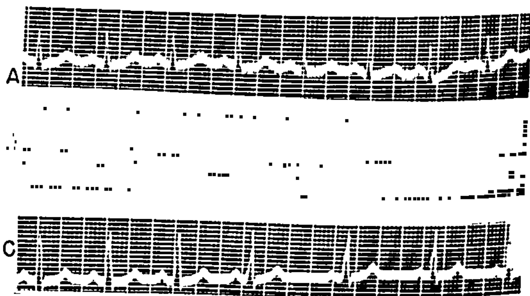


Fig. 11-1. Modifications of the heart rate and rhythm due to the SA node and revealed by the ECG. A. Sinus tachycardia. B. Sinus bradycardia. C. Sinus arrhythmia.

cardiac muscle and on the vagus nerves) is involved. This is also true for digitalis.

A paralysis of the accelerator nerve is possible in some cases, as a result of a central or peripheral lesion, but this is the least frequent mechanism.

Signs and Symptoms. Symptoms are usually absent, but a *further strong stimulation* of the vagus (sudden immersion in cold water, emotion, or pain) may cause *fainting* In such a case, a vascular collapse is frequently associated with the bradycardia.

The pulse is slow and regular but may present marked respiratory arrhythmia. The heart sounds and the pulsations of the jugular veins are normal

The *systolic blood pressure* may be normal or slightly low and is usually accompanied by a large pulse pressure

Graphic Methods. ELECTROCARDIOGRAM. The electrocardiogram is normal and shows a long diastole The P-R interval is normal. The rate is usually between 65 and 50, and only exceptionally between 50 and 40 (Fig. 11-1B)

PHARMACOLOGIC AND FUNCTIONAL TESTS The most important is the *atropine test*. Injection of 1 mg atropine sulfate hinders the action of the vagus nerve and accelerates the heart rate Another pharmacologic test involves the *inhalation of amyl nitrite* This is particularly effective in patients with coronary heart disease and bradycardia caused by functional depression of the SA node

Changes of position, exertion, and deep *respiration* are usually sufficient to accelerate the pulse in persons with sinus bradycardia Compression of the *carotid sinus* may arrest the heart in patients with bradycardia *due to* hypersensitive carotid receptors Both this maneuver and compression of the eyeballs may also arrest the heart in patients with an excitable *vagus nerve*

Diagnosis. Diagnosis is not difficult in most of the cases Clinical data are *usually sufficient* and may be supplemented by the *functional* and pharmacologic tests The electrocardiogram may be needed in doubtful cases or when the rate is very slow

Differential diagnosis should be made from *nodal rhythm, type 2:1 AV or SA block*, and complete AV block In the latter, there *is* usually a slower pulse, but patients with congenital AV block may have a pulse between [illegible]

Treatment. No treatment is required in most cases. If possible, the cause of the bradycardia should be removed.

In some cases, *atropine, ephedrine, Benzedrine, caffeine,* or *nitrites* will be required. Nitrites are useful *only* in patients *with coronary* heart disease

SINUS ARRHYTHMIA

Cause. This common irregularity of the pulse is usually associated with respiration. It is particularly evident in children, convalescents, or persons with unusually high excitability of the vagus nerve. It is also frequently present when *pleuropericardial adhesions* are *stretched by respiratory movements.* It may occur in old people with arteriosclerotic lesions and coronary heart disease, and in children with rheumatic carditis.

Signs. The pulse is periodically and alternately rapid and slow Slowing down of the pulse may be abrupt *but is usually gradual* in onset. The pulse may seem intermittent in the first case *These changes* of the heart rate are connected with respiration, *the phase of* rapid pulse occurring in the second half of inspiration and that of slow pulse in the second half of expiration

Deep breathing accentuates the phenomenon, *suspension of respiration* causes its disappearance. *Atropine* usually abolishes sinus arrhythmia

Graphic Tracings. ELECTROCARDIOGRAM. The electrocardiogram has normal waves, it shows, in general, gradual changes in the length of diastole (Fig. 11-1C). If there are sudden changes and the long diastole is equal to twice *the* P-P *interval*, the cause is SA block.

ARTERIAL TRACING The pulse waves become gradually larger and have a lower starting point, then become smaller *again*, with a higher starting point. This indicates *higher* systolic and lower diastolic pressures during the phase of slower pulse, usually during the *second half of expiration*

Mechanism. The various mechanisms of sinus arrhythmia are *illustrated* by the following scheme.

SINUS ARRHYTHMIA

Vagal:	Myocardial:
Respiratory	Incomplete SA block
Hypoxic (bulbar)	Type I *(periodic)*
Independent	Type II (intermittent)
	SA standstill

Diagnosis. The diagnosis can be made by means of the simple tests already described. Suspension of respiration causes a disappearance of the phenomenon. Atropine can be used in doubtful cases.

Differential diagnosis should be made with SA block. *Periodic SA block* may be connected with respiration and may be affected in the manner of respiratory arrhythmia by the functional tests. However, in SA block, *the long pause is equal to twice the short one;* in respiratory arrhythmia, the long pause is *less than double;* the increase is gradual in the latter.

Prognosis and Treatment. Prognosis is favorable except in those cases where the irregularity reveals an initial cardiac failure (coronary heart disease or acute rheumatic carditis. Therefore, correlation between sinus arrhythmia and all other clinical data is necessary.

No treatment is necessary. Atropine may cause disappearance of the disturbance.

2

Paroxysmal tachycardia

MAX HOLZMANN

Paroxysmal tachycardia is the name given to paroxysmal episodes of rapid heart action with sudden beginning and sudden end. Thus, the term is used in both a general and a limited sense, depending upon whether *acute episodes of atrial fibrillation* and flutter are included or not. The classification below gives an over-all picture of the various groups as revealed by the electrocardiograph.

HISTORICAL INTRODUCTION

According to Willius and Dry, Williams (1835) first described a case of paroxysmal tachycardia. Payne-Cotten (1667) published a typical case observation. A penetrating analysis of the disease was given by Bristowe (1888), and Bouveret (1889) separated out the paroxysmal rhythmic types from the numerous other forms of tachycardia, and coined the term used at present. Finally, Hoffmann (1900) published a well-known monograph on this syndrome.

With the help of the electrocardiogram, it was possible to separate paroxysmal tachycardia from paroxysmal atrial fibrillation or flutter. The discovery of the ventricular tachycardias was due to the use of the electrocardiograph. As a result, T. Lewis (1909) was able to describe short episodes of ventricular tachycardia in a patient and to produce ventricular tachycardia in a dog by means of coronary artery ligation. Robinson and Hermann (1921) demonstrated that, in man also, ventricular tachycardia can be caused by occlusion of a coronary artery.

DIFFERENTIATION OF THE PAROXYSMAL TACHYCARDIAS

The classification of the entire entity is based partly on clinical findings and partly on the electrocardiographic picture.

CLASSIFICATION OF PAROXYSMAL TACHYCARDIAS

Paroxysmal tachycardia *in a strict sense*.
- Essential paroxysmal tachycardia (Bouveret-Hoffmann type).
  - Supraventricular:
    - Rapid
      - With AV block
      - Without AV block
    - Moderate
  - Ventricular
    - *Rapid*
    - Moderate
- Extrasystolic paroxysmal tachycardia (Gallavardin type)
  - Supraventricular
  - Ventricular

Paroxysmal atrial flutter
Paroxysmal atrial fibrillation

Clinically, the classical form of paroxysmal tachycardia is revealed by the sudden occurrence of a regular and rapid heart action at 150 to 220 beats per minute (occasionally higher rates were encountered). In adults, the rate is usually below 200, while in infants and small children, it can exceed 300. In addition to the *rapid form of paroxysmal tachycardia*, a less common, *moderate form* can be observed, with a rate of 120 to 135 per minute. The uncomplicated cases are generally typical on account of the remarkable regularity of the rhythm. Two different entities can be separated clinically but without sharp differentiation:

1. The classical *paroxysmal tachycardia* (*Bouveret-Hoffmann type*). It is characterized by the sudden and unexpected onset of a regular tachycardia and by an equally sudden ending, while between *attacks, the heart* action is slow and regular or presents, at most, occasional premature beats.

Diagnosis. The diagnosis can be made by means of the simple tests already described. Suspension of respiration causes a disappearance of the phenomenon. Atropine can be used in doubtful cases.

Differential diagnosis should be made with SA block *Periodic SA block* may be connected with respiration and may be affected in the manner of respiratory arrhythmia by the functional tests. However, in SA block, *the long pause is equal to twice the short one,* in respiratory arrhythmia, the long pause is *less than double,* the increase is gradual in the latter

Prognosis and Treatment. Prognosis is favorable except in those cases where the irregularity reveals an initial cardiac failure (coronary heart disease or acute rheumatic carditis. Therefore, correlation between sinus arrhythmia and all other clinical data is necessary.

No treatment is necessary. Atropine may cause disappearance of the disturbance.

ble that they are also instigated in a similar fashion. In general, there seems to be a great variety of favoring elements. Physical exertion, certain body positions, gastrointestinal distention, constipation, pain in remote parts of the body, or emotion are the most common triggers. A relationship to body position is occasionally demonstrated In an unusual case described by Fine and Miller, atrial tachycardia began while the patient was in the erect position, had a higher rate while he was standing, a more moderate one while he was sitting, and was even less rapid when the patient was lying down, until it finally disappeared

SYMPTOMS The onset of the tachycardia is often recognized by the patient through an awareness of the heart Most patients feel a slight *pressure* on the chest, often a slight degree of *dyspnea* If cardiac dynamics are increased because of associated disease (hyperthyroidism, aortic insufficiency), the rapid pulsations become powerful On the other hand, the rapid rate can be completely unknown to the patient The author discovered paroxysmal tachycardia at a rate of 200 in an ambulatory patient with aortic insufficiency, the patient had no idea of its presence Wenckebach and Winterberg reported a case of a woman who consulted her physician only because she was disturbed, while in company, by visible pulsations of her neck vessels

The rapid heart activity can be felt as palpitation of the precordium or as pulsations in the neck or head Nausea, sweating, tinnitus, and faintness may occur The attack may be associated with an urge to urinate Less frequently, palpitation is associated with *precordial pain* If it is of slight degree, the latter is not alarming However, if it is severe, the presence of coronary sclerosis must be considered Sometimes, there is a "status anginosus," which persists as long as the tachycardia. Under these conditions, the persistence of precordial pain, even for several hours, should not be accepted as evidence of an infarct If the pain still persists *after* the termination of the tachycardia, on the other hand, an infarct has probably occurred Occasionally, the end of the attack is particularly unpleasant. A *lightning-like pain* in the *cardiac region*, often with radiation to the left arm, or *vertigo*, or even loss *of consciousness* may terminate the [illegible] [illegible]e latter may be due to *cardiac arrest* lasting several seconds. Most often the patients cannot describe the end of the attack because *it is followed* by sinus tachycardia. After the attack, many patients feel tired and weak for hours; others, on the contrary, are immediately able to resume their activities.

OBJECTIVE FINDINGS During an attack of tachycardia, the examining physician should count the rate during auscultation of the heart, because the pulse count is often misleading. The *radial pulse* may be small and weak, may vary in fullness with respiration, may alternate, and may be uncountable or even imperceptible. Occasionally, *pulsus alternans* can be demonstrated by a sphygmomanometer (or a pulse tracing) even though palpation fails to reveal it.

Often, strong pulsations of the *jugular veins* are present. Wenckebach (1910) first recognized this phenomenon in the phlebogram and stated that it was caused by summation waves due to superposition of the A and C waves of the venous pulse. If the attack ended, the pulsations also disappeared. *Auscultation* of the heart is characterized by a similar duration of the interval between the two heart sounds, designated by Huchard as *embryocardia* In other cases, the 1st heart sound is much louder than the 2d, in fact, the latter may be imperceptible Then, the danger of counting only one-half the beats must be avoided Previously existing murmurs may disappear during the tachycardia, or a *rough systolic murmur* may be added. A final evaluation of the auscultatory findings of the heart, and the conclusions drawn from them, must therefore be delayed until the attack is over.

The evaluation of *heart size* is today based on *x-ray* findings, which can be interpreted correctly only through comparison with films taken between attacks In uncomplicated cases, it can be demonstrated that the heart becomes *smaller* during the attack, which is what one would basically expect since diastole is relatively more shortened than systole (Dietlen; Groedel, Vaquez and Bordet). This is especially noticeable during a prolonged attack, and then atrial dilatation occurs as a result of venous engorgement and ineffective atrial contractions, a fact which is particularly true for the right atrium. After termination of the attack, a return of the right atrium to normal size can be noted, although the size of the

2. *Paroxysmal extrasystolic tachycardia (Gallavardin type)*. Runs of tachycardia follow each other for various periods of time, while in the intervals, there are single or short series of extrasystoles. In this way, palpation of the pulse may give the impression of an arrhythmia. Among the subgroups described by Gallavardin, three deserve special mention:

a. *The excitable form of paroxysmal tachycardia ("tachycardie à centre excitable")*, in which the attacks are not completely without cause and are easily provoked by slight physical strain or psychic excitement. Sometimes, as a result, there are extremely numerous attacks, most of them brief. However, the heart does not return to a normal rhythm in the intervals because of the frequent premature beats. The extraordinary lability of this condition constitutes a serious drawback for the patient.
b. *The prolonged form of extrasystolic paroxysmal tachycardia ("extrasystolie à paroxysmes tachycardiques")* or "repetitive paroxysmal tachycardia" of Parkinson and Papp, which is distinguished by its persistence over long periods of time (even many years) with only short interruptions of extrasystoles. This form has no apparent cause.
c. *The terminal extrasystolic tachycardia* occurs in patients with advanced coronary insufficiency and represents a prefibrillatory stage of severe prognosis.

The *ECG* makes it possible to divide the various forms of paroxysmal tachycardia *according to their origin* into *supraventricular* and *ventricular*. It also permits one to evaluate irregularities of rhythm, if they occur. This differentiation is of particular interest for therapy.

The pulse rate permits a presumptive differential diagnosis, but whenever possible, it should be confirmed by electrocardiography. The distinguishing features of the various types can be described as follows.

In *essential paroxysmal tachycardia (Bouveret-Hoffmann type)*, the attack may last from a few seconds to several days. It is followed by completely normal rhythm. During the attack, there is a regular rhythm with a rate of from 120 to 220 beats per minute in adults, and often over 300 in small children. The typical attack of palpitation usually is in the range of 165 to 200 in the adult.

In *extrasystolic tachycardia (Gallavardin type)*, there are occasional short runs of extrasystoles, and the attacks can follow each other with short pauses for a long period of time. The rate is somewhat lower, ranging from 125 to 190, and the rhythm is often not so regular as in the previous type.

The ventricular form of tachycardia may be transformed into dangerous attacks of *ventricular flutter* (regular rate over 300) or *ventricular fibrillation* (irregular rhythm).

The regular forms of atrial flutter are associated with a much more narrowly limited ventricular rate, which with a 1:1 conduction lies at 195 to 220, and with a 2:1 conduction, at 130 to 150. Therefore, a differentiation is often possible.

The *frequency range of the tachyarrhythmias* is in contrast very large, and stretches from an upper limit of about 215 down to the normal range, in which it loses its paroxysmal aspects. This range is determined mainly by the variable AV conduction in *atrial fibrillation, atrial flutter*, and *extrasystolic tachycardia*.

SUPRAVENTRICULAR TACHYCARDIA

Under this designation are grouped all paroxysmal types which have their origin in the region of the atrium or in the AV node. These, in turn, should be divided into *sinus, atrial*, and *nodal* tachycardia. The occurrence of paroxysmal sinus tachycardia has not been demonstrated. According to the view of most of the current authors (Scherf and Schott, 1953, Bellet, and others), nodal (AV) tachycardia is rare. *Supraventricular tachycardia is usually caused by an atrial ectopic focus.* For this reason, these forms are often grouped together under the name of "atrial" tachycardia. The term chosen here, however, is preferable because it includes all the possible forms.

The Clinical Picture. In general, the patient with a typical form of paroxysmal tachycardia experiences an attack in a completely unexpected manner. He is usually in a normal state of health and may be asleep. Exceptionally there is a *premonitory warning*, usually a general feeling of malaise hours or days before

ble that they are also instigated in a similar fashion. In general, there seems to be a great variety of favoring elements Physical exertion, certain body positions, gastrointestinal distention, constipation, pain in remote parts of the body, or emotion are the most common triggers. A relationship to body position is occasionally demonstrated In an unusual case described by Fine and Miller, atrial tachycardia began while the patient was in the erect position, had a higher rate while he was standing, a more moderate one while he was sitting, and was even less rapid when the patient was lying down, until it finally disappeared

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rest of the heart increases. In paroxysmal tachycardia of long duration (or with a damaged myocardium), a *globular cardiac enlargement* can be observed. This indicates that the contractile strength of the ventricles is poor, so that the diastolic residual blood is increased even in the ventricles. After the attack, the dilatation of the heart regresses.

The enlargement of the heart is often associated with a widening of the large veins due to engorgement, particularly apparent in the region of the superior vena cava.

The *stroke volume* is greatly decreased in paroxysmal tachycardia. Barcroft et al., in two cases having a rate of over 200, found the stroke volume decreased from 77.5 to 12.9 cm^3, and the cardiac output from 5 to 6 liters to 2.1 to 2.8 liters/min. The elevated heart rate therefore cannot compensate for the decreased stroke volume, and the output is diminished to one-half or one-third of normal. The decrease of stroke volume can be explained by the inadequate filling of the ventricles. While at a rate of 50, diastole lasts twice as long as systole, at a rate of 150, it lasts only one-half as long as systole. With further increase of heart rate, as a result of *the relationship between heart rate and length* of diastole, theoretically a critical rate could be attained, in which the entire cycle would be occupied by systole. According to Bazett's and Hegglin-Holzmann *formulas*, this rate would lie between 260 and 370. Other factors render the attainment of such rates impossible in adults. The heart size plays a certain role because small human hearts with a high resting rate can tolerate remarkably well further increases in rate, while large hearts with a slow basal rate withstand relatively poorly lesser increases. Under otherwise normal conditions, the maximum tolerable rate is about three times the resting rate of a heart (v. Boros).

BLOOD PRESSURE. Usually there is a moderate drop of systolic pressure and no change of the diastolic pressure. This can be explained by the frequency of small pulse waves, obviously connected with short intervals, during which less of a diastolic drop is possible. The *coronary flow* is adversely affected by the paroxysmal tachycardia because the duration of diastole, during which a large part of flow takes place, becomes especially brief. The lowered aortic pressure is a further cause of deterioration.

Wégria and Keating induced paroxysmal tachycardia in a normal dog and observed a temporary backflow in the coronary vessels and a drop of the mean pressure. In moderately rapid tachycardias, both returned in a short time to the initial values or (uncommonly) even exceeded them. With very high rates, however, they remained low for the duration of the attack. The rates being equal, coronary flow and mean pressure are more severely decreased in ventricular than in supraventricular tachycardia. After termination of the tachycardia, mean pressure rises first and may become higher than normal.

Peripheral circulation is usually poor. Patients are pale and their extremities are cool. If there is concomitant heart disease and the attack is prolonged, cyanosis and venous engorgement are common.

Poor systemic circulation is followed by inadequate oxygenation of the blood and may be revealed dramatically by *Cheyne-Stokes respiration*. This disturbance may occur early in patients having heart failure, or, if there is no heart disease, it may be provoked only by episodes lasting several days.

A characteristic phenomenon is a *sudden, profuse diuresis*, which occurs at the end of an attack. The urine has a light color and a low specific gravity. This urinary flow may also occur in tachycardia associated with atrial fibrillation or flutter.

Blood gas analysis during an attack was made by Carter and Stewart, as well as by Dieuaide et al. They observed a moderate decrease of oxygen saturation in the arterial blood and a severe decrease in the venous blood. Accordingly, *the arteriovenous oxygen* difference was greatly increased.

A relationship between paroxysmal tachycardia and epilepsy was considered long ago. More recently, accurate studies were made with the aid of the EEG (Gérard, Naquet, Gras, and Jouve). In three EEGs taken during paroxysmal tachycardia, an increase of the rapid waves seemed likely, and there was a tendency to alleviation of the alpha waves. Between attacks, whatever the type of tachycardia, nothing could be seen in one-half the cases, and in the other half, there were only slight variations, such as absence of alpha waves. Specific changes similar to those of epi-

lepsy were not established either during an attack or in the intervals.

The Electrocardiogram. The ECG is, as a rule, characterized by the regular succession of ventricular complexes of supraventricular origin, usually with normal QRS duration and of normal pattern, at a rate of *150 to 220 in* the typical form, and of 120 to 150 *in* the moderate type. *The atrial waves have the same rate as the ventricular and have a constant relationship to the latter.* The configuration of the P waves is variable according *to* the origin in higher or lower parts of the atrium, as in atrial premature contractions (Fig. 11-2). In general, the *P* waves reveal that the stimulus is conducted in an upward direction. When no P waves are visible, they may be buried *in* the QRS complex or in the T wave of the preceding cycle. When the P *wave is hidden by the QRS* interval because of simultaneous activation of the atria and ventricles, there is an AV (nodal) origin of the stimulus. When the P wave is hidden in the T wave, there usually is delayed stimulation of the atria. These situations, as well as the difficulty of differentiating whether a negative P wave belongs to the preceding or the following cycle, have led to the adoption of the general term of "supraventricular tachycardia" instead of "atrial" or "nodal tachycardia." A differentiation often can be made only when one can observe the onset of an attack. If this begins with a ventricular complex *followed by a negative* P wave in lead II or III, or without any P wave, there is a nodal pacemaker.

In the form of extrasystolic paroxysmal tachycardia, the relationship of the atrial and ventricular complexes is basically *the same.* At the termination of the attack, *premature* contractions often occur. They have the same pattern as the complexes of the tachycardia. It is impossible to draw a sharp line of division *between a premature* contraction with repetitive formation and an extrasystolic tachycardia. In general, a run *of more than 6 to 10 extrasystoles is called* extrasystolic tachycardia.

The *relationship* between P waves and *ventricular complexes is similar* to that found in atrial, nodal, and ventricular extrasystoles. The *ventricular complexes* differ more or less from those of the normal sinus rhythm because of *slight flattening of the T wave and depression* of the S-T segment. Not infrequently, however, a *significant S-T* depression is noted and should be interpreted as the result of a *relative coronary insufficiency.* As this occurs also in young and healthy patients, it is not indicative of coronary artery disease. While precordial pain can be completely absent, a *typical ischemic pain* can be induced by the *tachycardia in patients with* coronary arteriosclerosis.

Occasionally, the ventricular complexes show an *alternating pattern* which usually involves both the form and the amplitude of the QRS complex.

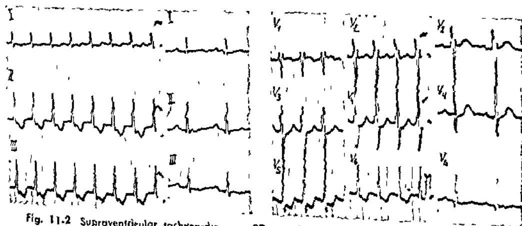


Fig. 11-2 Supraventricular tachycardia in a 37-year-old man without other abnormal cardiac findings. A After a 3-hr attack with a heart rate of 180. The position of the P waves can be established in lead V_1. B After an intravenous injection of 1.0 cm^3 of Mestinon and carotid sinus pressure, there is sinus rhythm at a rate of 95. Reflex slowing of the heart had been unsuccessfully tried prior to the injection.

In rare cases, the ventricular action may be irregular or slow, thus rendering the diagnosis particularly difficult. However the ECG will give the clue and solve the problem. The findings are.

1. *Irregularity of a supraventricular rhythm.* This is possibly connected with a variation of the P wave; it is usually the result of an extrasystolic type and is of moderate rate.

2. *AV conduction disturbances.* With changing rates, the conduction time can be slightly variable. If there is a 2° *AV block* with occasional dropping of stimuli, the picture of a tachyarrhythmia will take place. Poor AV conduction due to ischemia, infection, or digitalis glycosides predisposes to this picture. When there is a 3:1 or 4:1 type of block, the tracing may simulate that of atrial flutter. Finally, in complete AV block, the ventricular action is regular and slow.

3. *Addition of ventricular extrasystoles.* This occurs usually only at moderate rates, because otherwise the coupling is longer than the diastolic interval. There may be a combination of stimuli, so that ventricular activation is due partly to an extrasystolic focus and partly to a stimulus carried by the bundle of His. A rare occurrence is the combination of supraventricular and ventricular tachycardia

4. *Alternation* in the duration of AV interval is rare (10 out of 100 cases, Barker, P S, et al, 1943).

Complicated ECG findings can make the diagnosis of supraventricular paroxysmal tachycardia more difficult They may be the following.

1 *The patient already has a bundle branch block* This may give the impression of a ventricular tachycardia The problem is clarified only by the examination of previous or subsequent tracings Moreover, there are no P waves with a slower rate than the ventricular

2 *Intraventricular conduction disturbances* Strain of the ventricular conduction may cause variations of the intraventricular conduction, at times simulating the picture of bundle branch block It is important to note the constant relationship between the atrial and ventricular complexes The beginning of an attack is revealed by a premature P wave.

3 *Nodal tachycardia with interference dissociation* In a nodal tachycardia with retrograde block, it is possible that, occasionally, a P wave originating in the SA node finds the AV conduction system and the ventricles not in a refractory phase, thus resulting in a conducted beat. Since such ventricular complexes occur somewhat prematurely, they cause a slight arrhythmia. This sequence can be expected only in the type with moderate rate because of the longer refractory period of the ventricle (Schott, 1946).

Interpretation of the ECG can be clarified, at least in some cases, by *special observations* during and between attacks.

1. Observation, if possible, of the *beginning* or *end* of the attack, a feat which is less difficult in extrasystolic tachycardia than in the other types.

2. Depression of the rate or change of the conduction time, by means of *carotid sinus pressure,* so that the relationship of atrial and ventricular complex changes and P waves may be revealed. Blocking the AV conduction may reveal atrial flutter with rapid ventricular action. In atrial tachycardia, the P waves may appear, or the attack may be terminated.

3. The use of special ECG leads, particularly the *esophageal leads,* can reveal the P waves.

The *transition from paroxysmal tachycardia to sinus rhythm* (either spontaneously or following vagal stimulation) can occur in the following ways (Hellerstein and coworkers):

1. *A posttachycardic pause,* lasting several seconds and followed by sinus rhythm, is common

2 *The rate may become slower,* then suddenly change to a sinus rhythm

3 The transition can be *gradual.*

4. There is first a slowing, then a pause, and then the onset of sinus rhythm.

5 In the posttachycardic phase, one or more *nodal escapes* occur, then a few ventricular premature beats, possibly polyfocal, until sinus rhythm is reestablished.

Prolongation of the AV conduction and *aberrant ventricular response* can also occur.

The manner of termination of the attack is not always the same, even in the same patient. If during the tachycardia, there is a significant S-T depression, it usually disappears rather quickly However, if the sinus rate is still relatively high after the end of the attack, the depression lasts for a longer time After attacks lasting for several days, the ventricular com-

plexes often show some inversion of the T waves in various leads for several days or even weeks (*posttachycardial syndrome*).

Occurrence. Supraventricular paroxysmal tachycardia occurs at any age, however, it is relatively rare in newborn infants and young children There is no sex difference. Cases of familial occurrence have been reported.

The *frequency* of supraventricular paroxysmal tachycardia is difficult to determine, since some patients have never been checked during an attack, and others probably never realize that they are having an attack and therefore never report it

Kissane et al. analyzed the heart findings and clinical condition of 361 patients with supraventricular tachycardia, presenting the following data.

Percentage	*Finding*
34	No other illness demonstrable
34	Rheumatic heart disease
14	Arteriosclerotic heart disease
3	Hypertensive heart disease
5	Thyrotoxicosis
10	Other findings

The authors then compared these percentages with those of all the patients in their practice having these diseases From this, they realized that these attacks occur much more frequently in rheumatic than in arteriosclerotic heart disease, and that hyper- and hypothyroidism have no influence

The general experience is that, in at least one-third of the cases, the heart is normal

Mechanism. In order to explain paroxysmal tachycardia, we must consider the fact that the stimuli of either supraventricular or ventricular origin arranged in rapid sequence can occur with the same coupling as with individual extrasystoles No sharp distinctions can be drawn between runs of extrasystoles in series and paroxysmal tachycardia Therefore, premature contractions and paroxysmal tachycardia must have a similar mechanism

The theory of a *circus movement* was advocated by Mines Lewis refused to accept it in paroxysmal tachycardia His reasons were that it was not proved that extrasystoles were due to a circus movement, that the rate is lower than in flutter, that the stimuli were not necessarily arranged in series, and that no sufficiently long pathway was available in the atria to permit a circus movement at the necessary speed De Boer invoked the existence of the *bundle of Paladino-Kent* in order to explain supraventricular tachycardia. The stimulus would run upwards through the bundle of His and then over the accessory bundle back to the atrium, or in the opposite direction While this could be admitted in the Wolff-Parkinson-White syndrome, the explanation certainly is not valid for the other forms.

Ashman and Hull resorted again to the "circus" theory by admitting a *functional*, longitudinal dissociation in the bundle of His permitting both an atrial and a nodal pacemaker (in cases with retrograde conduction, possibly even a ventricular). A premature atrial beat would stimulate only part of the conduction system while the rest would still be in a refractory state. From the first group of fibers, *the stimulus would be transmitted* to the second and, through it, back to the atrium, which would again be stimulated.

The *theory of frequent heterotopic impulse formation* has more supporters today than the circus theory Scherf (1928, 1948, 1953), as well as Prinzmetal (1950, 1952), and their coworkers, have advocated this theory. The following points are presented in its favor:

1 In animal experiments, local application of barium chloride, digitalis, or strophanthin causes the formation of an extrasystolic focus. Warming of this focus is followed by paroxysmal tachycardia, which continues as long as the warmth is maintained (Scherf, 1948).

2. A circus movement within the atria is excluded because of the relationship between period length and speed of spread on the one hand, and length of the available path on the other (Lewis, 1925)

3 Sudden doubling or halving of the atrial rate (from 107 to 214—Camp and Scherf; a few observations from 90 to 180 and back) with unchanged P waves is compatible with a 2.1 exit block of the ectopic impulse.

4 The occurrence of an interference dissociation cannot be explained by a circus movement but is easy to explain by ectopic impulse formation (Schott, 1946)

Prinzmetal et al. (1950) provoked atrial tachycardia in the dog by means of chemical, electrical, and mechanical stimuli, and registered it on ECG moving pictures, and with the oscilloscope In all records, they found a spread of the impulse occurring in all directions. When they stimulated mechanically the atria of patients undergoing chest surgery,

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is unsuccessful. Bilateral compression of the carotid should not be attempted since it causes cerebral anoxia. Unconsciousness and convul-

sinus pressure apparently was followed by cerebral thrombosis

If this maneuver is ineffective, *ocular pressure* should be attempted Intense pressure below the supraorbital ridges on the downward turned eyeballs is usually painful and should not be attempted on injured eyes. It causes a powerful *oculocardiac reflex.*

The success of these measures depends upon the skill of the operator and the type of attack. Success is claimed by various authors in from 10 per cent (White) to 80 per cent (Bellet) of cases If one of these methods works and the patient suffers frequent attacks, it is recommended that either he or the people around him be instructed in the use of the maneuver

MEDICATION *Parasympathomimetic drugs* Individual sensitivity to these drugs varies strongly Unpleasant side effects, such as nausea, vomiting, salivation, sweating, hyperpnea, and drop in pressure, can occur For these reasons, the following precautionary rules should be followed when these drugs are to be given by injection

1. The application should always be made with the patient lying down

2 A hypodermic syringe containing 0 5 to 1 0 mg *atropine* as an antidote should be ready for intravenous injection

3 Bronchial asthma and coronary sclerosis are contraindications

As all these drugs sensitize the vagal receptors, reflex vagal stimulation may become successful if tried a few minutes after their administration *Physostigmine*, 0 5 to 1 5 mg subcutaneously, has been used by Kaufmann (1912) (in combination with digitalis) and by de Meyer (in combination with strophanthin)

Prostigmine (*neostigmine*), 0 5 to 1.0 mg subcutaneously or intramuscularly, has proved successful (Waldman and Pelner) Intravenous administration should be avoided because dangerous The oral route is less reliable Abdominal cramps and diarrhea are common side effects.

Mestinon (pyridostigmine bromide), 1.0 to 2 0 mg intramuscularly, or 1 mg intravenously, or 20 mg four times a day orally, has a milder action.

Acetylcholine was recommended by Segers and coworkers (1945) as follows: intravenous injection of 20 mg (1.0 ml of 2 per cent solution), if this is without effect, the injection is repeated every 3 to 4 min with increasing doses of 40, 60, and 100 mg, as necessary. The effect usually occurs within 30 sec. Because a significant drop in blood pressure can occur, the patient should be supine and a syringe containing 0 5 to 1.0 mg atropine should be available.

Doryl (Merck) (carbaminol-choline-chloride) has been recommended similarly for intravenous injections (Birk, Lethaus, and Plugge). If ½ ampule (0 25 mg in 1 ml) is not sufficient, it can be repeated after a short time. The injection must be given very slowly in order not to cause a prolonged cardiac arrest.

Acetyl-beta-methylcholine (*Mecholyl*) was recommended by Starr (1933, 1936) and by Morgan in subcutaneous doses of 10 to 50 mg (average 25 mg). It is claimed that it terminates 90 per cent of the attacks. It should *not* be given intravenously. Its action becomes manifest within a few minutes. Side effects are more frequent and more severe than with acetylcholine, and even fatalities have occurred. With the transition to sinus rhythm, a short ventricular tachycardia of the fibrillatory type can occur (Bellet).

Strophanthin may terminate an attack immediately after one intravenous injection of 0 75 mg (Volhard), or one to two injections of 0 5 mg or three to four injections of 0.3 mg (Edens and Weese). Possible dangers of such large doses should be considered, especially if there has been previous digitalization or if the patient has coronary sclerosis.

Digitalis preparations are preferred today in the treatment of supraventricular paroxysmal tachycardia (Wilson and Wishart; Bohnenkamp). Intravenous injection of 0 8 to 1 6 mg *Cedilanid* can result in a sudden interruption of the attack (Kroetz) or in its arrest within 20 min (Weissberger and Feil). A similar effect can be obtained with *digitoxin* or *acetyldigitoxin* (*Acylanid*) in dose of 1 3 to 2 0 mg in one to two intravenous injections (Spang, Loeffler et al).

they repeated the same observations for both extrasystoles and tachycardia.

Pathologic Findings. Occasional deaths of patients with supraventricular tachycardia have revealed gross anatomic findings corresponding to the accompanying disease. In other accidental deaths, these findings have been absent. Precise histologic examinations are rare. Most of the studies have revealed changes in the area of the SA node, the atria (especially the right), the AV node, and the bundle of His.

Mackenzie (1908) described a case with obliteration of the nutrient artery of the AV system, and a case with fibrotic changes in the SA node. Cade and Rebattu (1911) described a case with round cell infiltration and connective tissue hyperplasia in the bundle of His. Butterfield and Hunt studied a case with cell infiltration of the wall of the right atrium, including the SA node. Falconer and Duncan examined the heart of a case with interstitial lymphocyte accumulation in the right atrium, SA node, and AV node area Mahaim (1932) studied a 14-month-old child who had suffered from an uncontrollable supraventricular tachycardia following influenza. In the right atrium, widespread foci of lymphocytes and polymorphonuclear leucocytes, which had involved the SA node region, were found Piotti (1945) studied an 11-month-old child, who had suffered from a sustained supraventricular tachycardia for 7 months, and found interstitial myocarditis (Fiedler type) involving the right atrium and particularly the area of the coronary sinus

Prognosis. The prognosis of the supraventricular tachycardia is usually good Death during an attack is rare However, it may occur in cases with myocarditis or coronary heart disease.

The prognosis should be guarded if a serious heart condition is present, particularly coronary heart disease. If the blood pressure is low, the dangers represented by prolonged or frequent attacks are greater Among other complications, thromboembolic phenomena may occur In these cases, the prognosis is based upon the speed and efficacy of treatment.

In normal hearts, even prolonged and frequent attacks are well tolerated. Noteworthy are the cases in infants and adolescents who may have prolonged extrasystolic tachycardia lasting even 10 years without permanent damage and finally disappearing.

The *life expectancy* is not shortened by paroxysmal tachycardia in an otherwise normal heart. Campbell and Elliot found among 100 cases, 3 who experienced paroxysmal tachycardia for longer than 50 years, and 18 who had it for longer than 20 years. Cooke and White observed a man, still active at 72, who had suffered attacks of paroxysmal tachycardia since the age of 7. It is possible that paroxysmal tachycardia which starts at an older age should be considered more seriously. While Campbell and Elliot admit this point, Cooke and White (1942) find no difference in the prognosis whether the first attack occurred before or after the fortieth year of age.

Treatment. Medical management has two objectives: cessation of the attack and prevention of its repetition.

The treatment of the attack is frequently successful in the supraventricular paroxysmal tachycardia and is based on *reflex stimulation of the vagus nerves.* Often the patient himself has discovered certain means of depressing the attack and the physician can use similar methods. If they do not succeed, he can resort to well-known methods of vagal stimulation If these also fail, certain drugs are available which will either stop the attack or act within a short period of time. In the greatest number of cases, these means are successful, reflex stimulation should always be tried first If one resorts to medication, one should begin with the most harmless.

THE MECHANICAL REFLEX INFLUENCES Certain methods have been shown to be of benefit in individual cases These are curling of the body, lying down with the head below the level of the body, strenuous tensing of the abdominal muscles, the Valsalva or Muller maneuvers, production of nausea by stimulation of the palate, or drinking of iced water. If these measures do not suffice, stronger *reflex vagal stimuli* should be attempted Since before the establishment of a sinus rhythm, a significant "preautomatic" pause can occur, with at times a cardiac arrest of a few seconds, these measures should always be undertaken with the patient lying down

Carotid sinus pressure is in general the most effective It should be done with constantly increasing intensity while monitoring the heart action and should be discontinued as soon as the tachycardia disappears, so that an unpleasant cardiac arrest will be avoided. First, one should try one side, then the other. Repeated stimulation of the same side generally

VENTRICULAR TACHYCARDIA

The Clinical Picture. In contrast to the supraventricular form, these attacks, as a rule, occur in individuals having cardiac disease They are, therefore, only part of the clinical picture, may be unrecognized by the patient, and often are not properly evaluated by the physician, at least in a first period.

The duration of the attack may vary. Most episodes last from a few seconds to several days Attacks lasting from 3 to 4 weeks are not unusual The longest ventricular tachycardia, lasting 77 days, was described by Mays

If an episode of ventricular tachycardia has occurred once, *there is a tendency for its repetition* These attacks can occur either after brief intervals or, on the contrary, only after several years They may tend to become more frequent with time On the other hand, there may be a single episode—e g , after a coronary occlusion, followed by permanent recovery or, at times, having a fatal outcome

Symptoms and Signs They vary considerably according to the underlying heart disease and the duration of the attack If there has been heart failure, ventricular tachycardia may be completely unapparent and masked by the general picture If the attack lasts for several days, increasing signs of circulatory insufficiency, such as *dyspnea, somnolence,* and *pain in the right hypochondrium,* often occur If the attack follows an infarct, either a *status anginosus* (persistent precordial pain) or a sudden *collapse* may be the consequence

Occasionally, certain clinical *signs* indicate the nature of the tachycardia They are not always present, however, and at times may be doubtful, so that the final diagnosis is always made through the ECG.

The ventricular rate can be determined by simultaneous auscultation of the heart and palpation of the pulse It is usually between 160 and 180, but it may be as low as 125, particularly under the influence of medication On the other hand, if ventricular flutter occurs, the rate may exceed 200

The cardiac rhythm may be completely regular Several authors (particularly Strong and Levine, S A , 1927) emphasize that ventricular tachycardia is less stable than the supraventricular However, they most likely refer to cases of extrasystolic tachycardia with short pauses, during which single extrasystoles occur. In these cases, one has the impression of a considerable arrhythmia, even simulating that of atrial fibrillation.

On auscultation, *the heart sounds show different degrees of loudness if the atria are still ruled by a SA pacemaker.* Levine (1921) showed that the 1st heart sound presents periodical changes of intensity. As in complete AV block, the 1st heart sound is louder (*cannon sound*) if the atrial and ventricular contractions occur at the same time or if the atria contract 0 05 to 0.12 sec before the ventricles (Duchosal). Obviously, this phenomenon does not occur if there is atrial fibrillation or retrograde atrial stimulation Apart from these cases, periodic intensification of the 1st sound is demonstrable in about 50 per cent of the cases (Armbrust and Levine).

Another phenomenon occasionally determined at auscultation may be *misleading: only* the 1st sound may be heard, or even more misleading, its loudness may alternate (Armbrust and Levine) Then, it is possible that only *one-half* of the ventricular beats are counted. The peripheral pulse can *sometimes* clarify the situation, the ECG always does so.

The *arterial pulse* is mostly small and often difficult to palpate Occasionally, it shows a *periodic intensification* If one can exclude any connection with respiration, such a finding is typical of ventricular tachycardia. The larger pulse waves occur when an atrial contraction falls at the end of a ventricular systole or with a short ventricular diastole, while the pulse is small or absent if the onset of the atrial contraction occurs at the beginning of a ventricular systole (Fischer; Lian et al., 1931; Zeh) When an atrial contraction occurs simultaneously with a ventricular, it forces the blood backwards into the large veins and there is less venous return shortly thereafter, so that the subsequent ventricular filling is decreased. In cases with dissociation, the arterial pulsations were recorded graphically and found to be decreased when the R-P interval was between 0 06 and 0.18 sec.

In the *venous tracing,* a tall wave can be observed at the time of the "cannon sound" (Gallavardin, 1920) Careful inspection of the jugular veins reveals pulsations which occur at about *one-half* the rate of the ventricular systoles as determined by auscultation, and

Because the digitalis, in addition to its direct action on the heart, decreases the threshold of the carotid sinus, it is worthwhile to press the carotid sinus again 20 to 30 min after the injection, in case the desired result has not occurred. This should always be tried before further digitalis injections are given. Digitalis therapy is indicated if the tachycardia occurs in a damaged heart or in the presence of congestive failure, and if the reflex vagal stimulation was unsuccessful.

Quinidine acts by depressing all properties of the heart. It should not be used if there is heart failure but can be resorted to in other cases if carotid pressure and digitalis have failed. Quinidine is given orally as *quinidine sulfate* in dose of 0.4 Gm four to six times daily. If the oral route cannot be used or rapid action is necessary, *quinidine gluconate* 0 4 Gm can be given intramuscularly (Bellet) and repeated after 2 hr if necessary. The intravenous approach is not advisable because of possible unpleasant side effects

Magnesium sulfate acts like quinidine; 10 to 20 ml of a 20 per cent solution can be injected intravenously within ½ to 1 min (Zwillinger, Boyd and Scherf) The injection is accompanied by a sensation of warmth and can be followed by a significant drop in blood pressure. Before the end of the tachycardia, conduction disturbances and ventricular extrasystoles may occur With severe myocardial damage and intraventricular conduction disturbances, magnesium sulfate should be avoided.

Procaine amide (Pronestyl) is similar in action to quinidine It is especially indicated in ventricular tachycardia but has been recommended also in supraventricular tachycardia. According to Bellet and coworkers (1952), it is effective in 80 per cent of the cases.

Sedatives with sympatholytic action have been used (Szutrély and Voltay) One mixture is the so-called "*lytic cocktail*" of Laborit and Huguenard, which is composed of Largactil/Phenergan/Dolantin in the ratio of 1:1:2 and is given intravenously at an approximate dosage of Largactil of 0.6 mg/kg.

Sympathomimetics, like *Neo-synephrine,* are occasionally effective This illuminates the multiple influences which are possible. The sympathicomimetics stimulate the carotid sinus through a blood pressure rise and thus produce vagal stimulation. In case 0.5 mg intravenously does not work, a double dose can be tried, except in cases of hypertension and coronary sclerosis (Youmans and coworkers).

Other drugs have been used occasionally but have no practical importance They are *adenosine* (Kalaja), *fagarine*[1] (Scherf et al, 1949, Silver and Weinberg; Taquini), *Veratrum viride* (Shaw), *calcium gluconate* (Wolffe and Bellet), *Atabrine* (Gertler and Yohalem).

Surgical procedures have been attempted in patients with a great frequency of attacks. Leriche et al. (1935) recommended *left stellectomy.* According to White and Bland, the ganglion chain should be removed bilaterally from the stellate ganglia downwards to the fourth or fifth thoracic ganglion. *Alcohol injection* into the ganglia can be effective, but the attacks may recur after regeneration of nerve fibers (Coleman and Bennett).

PROPHYLACTIC MEASURES FOR THE PREVENTION OF ATTACKS. When any precipitating factor is known in a particular case, such as overeating, alcohol, smoking, coffee, constipation, certain body positions, or psychic stimulation, it should be eliminated.

In resistant cases, *medical means* should be added. The same drugs which have been described to terminate an attack can be given in small doses for this purpose. Basically, the smallest dose which may prevent an attack should be used.

Of the *vagomimetics,* particularly good are *Doryl* or *Mestinon* in tablet form. It is recommended to begin with three tablets daily.

Digitalis is the drug of choice if the attack has not occurred under previous digitalization, and if heart failure is present

Quinidine is to be recommended in patients without heart disease. Association with phenobarbital often proves useful

Procaine amide with an initial dose of 250 mg three to four times, is also to be considered.

Rauwolfia alkaloids are not effective in terminating an attack but may be effective prophylactically. *Serpasil,* 0 1 mg, three to four times daily is the usual dose for children, 0.25 mg three to four times daily for adults (Bixby, Szutrély and Voltay).

[1] Fagarine may cause ventricular fibrillation and should not be used in clinical cases. *Editor.*

systoles between attacks as during an attack *indicates* ventricular tachycardia

The ECG can show other characteristics:

1. *Alternating ventricular complexes can occur.* There may be a *monophasic*, homolateral alternation consisting of changing amplitude of part of the ventricular complex, or a *diphasic*, bilateral alternation consisting of a change of polarity of the ventricular complex and indicating alternative pacemakers in the two ventricles (Fig. 11-4). The latter is encountered especially under the action of digitalis glycosides. The duration of the ventricular complex may be stable or alternate.

2. *The ventricular complexes may be polyform.* Then the ventricular action is generally irregular and, as a rule, is associated with atrial fibrillation (Fig 11-3A). These tachyarrhythmias represent a dangerous condition, which usually is followed by ventricular flut-

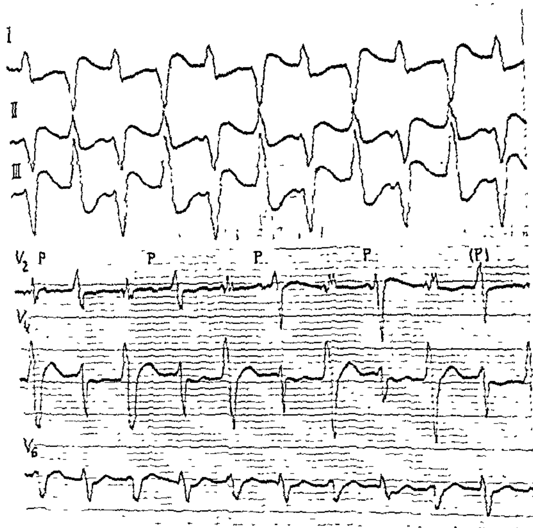


Fig 11-4. Paroxysmal alternating ventricular tachycardia in a 55-year-old man with decompensated hypertension after a 10-day treatment consisting of daily intravenous injections of 0.25 mg Strophosid, 0.25 Gm Euphylline, and 10 ml of 5 per cent glucose. Mean ventricular rate, 143 to 153. The phasic alternation is most marked in the limb leads The independence from a sinus rhythm is demonstrated by the "wandering" P waves in the precordial leads There is at times a definite alternation of the ventricular complexes The ventricular tachycardia disappeared after discontinuation of strophanthin. The patient died 2 months later. At autopsy, severe bilateral hypertrophy with fatty degeneration of the myocardium, a subacute infarct in the left papillary muscle, and renal arteriosclerosis were found.

which periodically increase and decrease in amplitude independently of the respiration. These pulsations will be revealed even better, however, by recording a *jugular tracing* and are due to superposition of the A and C waves.

The changes of *heart size, stroke volume,* and *blood pressure* are the same as in supraventricular tachycardia. During the clinical taking of blood pressure, a periodic increase of the pulse can occasionally be demonstrated (see above).

With the auscultatory method, arterial sounds are generally audible only at long intervals corresponding to a periodically increased systolic pressure. With the oscillometer, this phenomenon is designated as "nonalternating anisosphygmia" (Lian et al., 1931).

The effect of the tachycardia on the peripheral circulation is in general more severe than in supraventricular tachycardia because usually the heart is damaged Somnolence and Cheyne-Stokes respiration are more frequently observed. Exceptionally, tachycardia may be followed by gangrene of the fingers or toes (Abrahams).

The Electrocardiogram. The typical picture of ventricular tachycardia shows ventricular complexes similar to ventricular extrasystoles in rapid and regular (or almost regular) sequence; *there are P waves recurring at a slower rate* (Fig. 11-3B, C). The shape of the ventricular complexes in the various leads depends upon the site of the ectopic pacemaker, as in the case of extrasystoles For their recognition, the same methods should be employed. Theoretically, the tachycardia could originate in the basal portion of the ventricular septum or at the origin of the bundle of His, so that a normal pattern of ventricular stimulation could occur. Furthermore, the P waves can be absent if there is atrial fibrillation in addition to the ventricular tachycardia.

If the demonstration of a rapid ventricular rate, independent of SA stimulation, cannot be obtained, finding the same coupling for extra-

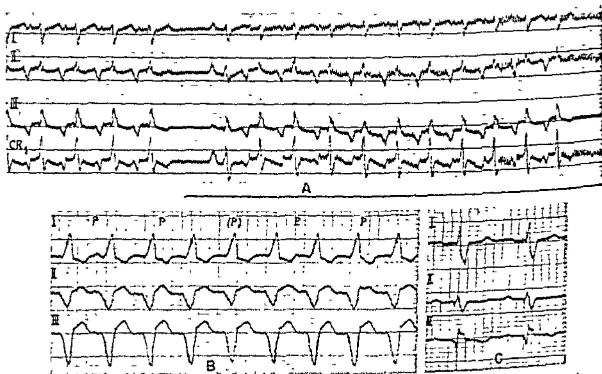


Fig. 11-3. A Supraventricular tachycardia in an 8-year-old girl Obstinate and frequent attacks. Inverted P waves in leads II, III, and CR_1 Because the AV interval is 0 14 sec, the pacemaker must be in the caudal portion of the atria With carotid sinus pressure (white flap), the tachycardia can be interrupted for short periods. However, after one ventricular complex of sinus origin, the attack starts again. B. Ventricular tachycardia in a 75-year-old man with a myocardial infarct. For 4 days there was a right ventricular tachycardia at a rate of 133. The P waves fall before, within, or after the QRS complexes at a rate of 70. C. Same case as in (B), after Pronestyl (0.5 Gm, four times). Sinus rhythm at a rate of 70, prolonged AV conduction, and right bundle branch block.

ter and fibrillation (*prefibrillatory phase of Gallavardin* or *ventricular anarchy of Clerc and Levy*).

3. If the ventricular stimuli follow each other in rapid sequence, so that their beginning and end can no longer be distinguished, and if, moreover, diphasic undulations occur, then ventricular tachycardia has become *ventricular flutter*.

4. A retrograde conduction to the atria, as a rule, does not occur; however, since no AV block is present, a *pararrhythmia* may arise, causing an *interference dissociation*. As a result of the high ventricular rate, and probably as a result of penetration of impulses into the lowest portion of the conduction system rendering it refractory, there is very seldom an AV conduction If such a conduction exceptionally occurs (particularly when the ventricular rate is moderate), it is revealed by a few premature ventricular complexes without the typical bundle branch block appearance, or by *fusion beats* when the rates are similar, so that the ventricles are stimulated partly through the bundle and partly by an ectopic ventricular focus (Holzmann)

5 In rare cases, a *retrograde conduction of the ventricular impulse to the atria can be observed*, similar to that which may occur in ventricular extrasystoles Then, negative P waves can be seen in leads II and III following the QRS complexes The retrograde mechanism becomes especially clear if the retrograde conduction is combined with a *second-degree retrograde block with Wenkebach periods*. Then, the ventricular complexes continue undisturbed while the negative P waves migrate farther and farther from the QRS complex until one is dropped and the sequence begins again (Fig. 11-6). In the *differential diagnosis* of this form, one should consider supraventricular tachycardia, as well as atrial fibrillation and flutter, with previous bundle branch block, or a functional bundle branch block caused by the tachycardia. Tracings recorded before the attack are, therefore, always extremely helpful.

If there is considerable variability of the ventricular rate, *atrial fibrillation with a functional bundle branch block* should be excluded before admitting a ventricular tachycardia. If atrial fibrillation with conduction to the ventricles was present prior to the attack, the assumption of ventricular tachycardia is justified by the appearance of an independent ventricular stimulation occurring *by attacks*. There are, however, cases of atrial fibrillation with severe variations in the AV conduction and with a threshold value of the conduction in the bundle, which causes this to become deficient if the rate is high The more regular and rapid the ventricular rate, the more likely is the assumption of ventricular tachycardia. This may be confirmed by finding ventricular complexes with the same coupling as that of extrasystoles between attacks.

Supraventricular tachycardia with a second-degree AV block can simulate runs of ven-

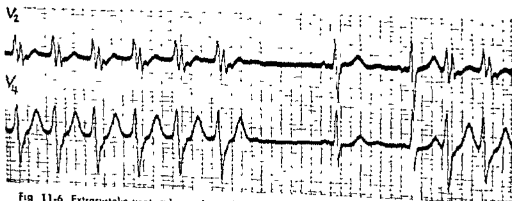


Fig 11-6 Extrasystolic ventricular tachycardia in a *62-year-old* woman, range from 143 to 153. Retrograde conduction to the atria with Wenckebach periods The *second* ventricular complex shows no retrograde conduction The RP measured 0.1[illegible]

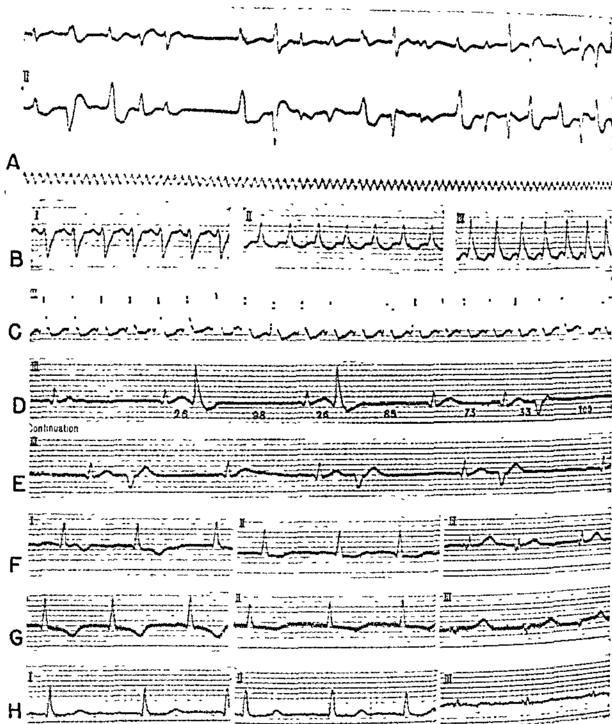


Fig. 11-5. A Complete ventricular anarchy in a woman, aged 60, who was suffering from chronic rheumatic carditis and circulatory failure (autopsy was performed 3 days later). Atrial fibrillation. Complexes of supraventricular origin (first and sixth) with variable ventricular conduction paths; ventricular tachycardia with irregular complexes. B. Left-sided ventricular paroxysmal tachycardia in a 50-year-old woman with myocardial disease of unknown origin. During the attack: ventricular rate, 227 C Immediately following intravenous injection of quinine hydrochloride, gr 7½ (0 5 Gm); ventricular rate, 240 Variable irregularities in the S-T segment suggest atrial fibrillation D. 40 sec later; atrial fibrillation. Marked abnormality of the ventricular complexes at irregular intervals, with ventricular extrasystoles. E 5 min later atrial fibrillation with myocardial damage, particularly of the left ventricle. F. 2 days later; ventricular complexes even more abnormal. G. 4½ months later; atrial fibrillation. Regression of posttachycardia syndrome. (*From Holzmann. Klinische Elektrokardiographie,* 1955.)

in chronically ill cardiac patients in the hospital

The attacks are favored by advanced age. While some cases have been observed in the second decade, most of them occur between 50 and 70 years of age

The *male sex* predominates, about two-thirds of the cases occur in males.

Ventricular tachycardia can occur either with sinus rhythm or with fibrillation. Exceptionally, it can also follow a supraventricular tachycardia (Barker, P S).

Usually, though not always, the attacks occur in patients with a severely damaged myocardium; in about one-half the cases, the clinical picture of congestive failure either exists or supervenes

In a statistical study of 107 cases of paroxysmal ventricular tachycardia, Armbrust and Levine found the following·

Finding	*No of Cases*
Coronary artery disease	79 (74%)
Rheumatic heart disease	9
Congenital heart disease	1
Wolff-Parkinson-White syndrome	5
No evidence of heart disease	13 (12%)

During *severe infections,* such as diphtheria, rheumatic fever, or streptococcal infections, ventricular tachycardia may be observed in children

Epinephrine and large doses of quinidine or *Pronestyl* can provoke attacks

Overdose of *digitalis glycosides* may precipitate ventricular tachycardia, and even moderate doses may do so in a severely damaged myocardium This is not astonishing, for digitalis favors the formation of ventricular pacemakers Since digitalis intoxication in normal individuals does not cause ventricular tachycardia, preexisting myocardial damage is essential in the causation of this disturbance

According to general experience, patients with an otherwise normal heart were encountered mainly in the younger age groups Campbell and Elliot found an apparently normal heart in 8 of 11 patients under 40 but in only 2 of 31 patients over 40 years of age

The following etiologic-clinical classification of the ventricular tachycardias is after Froment

1. *Ventricular tachycardia in cases with severe myocardial disease*
   a. *Cases with septal lesions.* They usually follow a recent myocardial infarction involving the septum, but may occur without it. Rarely they are due to syphilitic myocarditis involving the septum. They occur mostly in advanced age, and the ECG usually has a constant configuration. The prognosis is rather poor.
   b. *Cases with terminal, prefibrillatory tachycardia.* This form is observed in patients with severe congestive failure, often follows previous brief runs of tachycardia, and is revealed by a polymorphic aspect in the ECG. The prognosis is very poor.
2. *Ventricular tachycardia in clinically normal hearts·*
   a. *Extrasystolic type* (*extrasystolie ventriculaire en salves,* Callavardin) with onset during youth and with a course which may be either benign or obstinate, even lasting for more than 30 years.
   b *Essential type* (Bouveret-Hoffmann), with less frequent but longer attacks, which usually begin during youth and which may have a course of many years The prognosis is good.

Mechanism. The possibility of a circus movement cannot be admitted because there are no pathways between the ventricles The cases which present ventricular extrasystoles between attacks having the same coupling and pattern confirm that both the tachycardia and the extrasystoles have the same mechanism, i e , a heterotopic focus of impulse formation or a reentry phenomenon.

Pathology. Upon gross examination, there is no typical finding in cases of ventricular tachycardias However, lesions of the ventricular septum are rather frequently encountered, and microscopic lesions consisting of inflammatory or degenerative changes in the network of Purkinje or in the AV node, the bundle of His, and its branches are extremely frequent (Mahaim, 1932). It is logical to consider that these lesions represent the anatomic basis of the attacks of tachycardia. This assumption explains why not infrequently ventricular tachycardia and AV block release each other The former corresponds to a stimu-

tricular tachycardia, if several stimuli are conducted one after another, and cause a functional bundle branch block.

MOBITZ'S INTERFERENCE DISSOCIATION. A pararrhythmia of sinus and node activity with additional *functional bundle branch block* can be recognized because the prematurely conducted ventricular impulses also show the bundle branch block pattern.

Not infrequently, a definite decision as to the underlying mechanism cannot be made from a single ECG finding. Then, the following methods may be used:

1. *Reflex vagal stimulation* This barely influences ventricular tachycardia, or affects it not at all, whereas it may terminate supraventricular tachycardia (a functional bundle branch block would disappear), or so depress AV conduction that AV block occurs (the rapid atrial activity becomes visible) and fibrillation or flutter waves are unmasked.

2. *Esophageal leads* may clarify the relationship of the ventricles and atrial complexes by revealing the latter with a higher voltage.

3 *Pronestyl* can contribute to the diagnosis by overcoming a ventricular tachycardia

The *differential diagnosis* between supraventricular and ventricular tachycardia can be made, up to a certain point, by observing the characteristics of the rhythm, the heart sounds, the arterial and venous pulses and, above all, through the electrocardiogram. Reflex vagal stimulation can be informative (Table 11-1).

Occurrence. Paroxysmal ventricular tachycardia is rare in office practice, but it is often encountered during acute heart attacks and

TABLE 11-1 DIFFERENTIAL DATA OF THE TACHYCARDIAS

	Supraventricular	*Ventricular*
I Rhythm	A *Regular* (essential type) Exceptions—irregular with· 1. Second-degree AV block 2 AV tachycardia with interference dissociation B *Irregular* (extrasystolic type)	A *Either regular or slightly irregular* (essential type) B. *Severely irregular* (extrasystolic type)
II. Auscultation	First heart sound of constant loudness (may not be so in I A.)	First heart sound periodically increased (except with retrograde atrial stimulation or atrial fibrillation)
III Arterial pulse	Equal	May be periodically increased
IV. Jugular tracing	Constant large pulsations (may not be so in I A)	Periodical atrial waves (except that retrograde atrial stimulation will cause nonperiodic waves while atrial fibrillation will cause their disappearance)
V Electrocardiogram A Atrial complex	*P wave in constant relationship to the ventricular complexes* (except in the presence of block and in AV tachycardia with interference dissociation)	*P wave independent of the ventricular complexes* (except with retrograde atrial stimulation; the P waves will be absent if there is atrial fibrillation)
B. Ventricular complex	*Ventricular complexes of conducted type* normal QRS duration (except if there already is bundle branch block or if a functional bundle branch block is caused by the tachycardia)	*Bizarre ventricular complexes,* QRS interval prolonged and deformed (except if the stimulus originates in one stem of the [illegible] lation with a functional bundle branch block, and tachycardic atrial fibrillation with conduction through an abnormal AV pathway (Wolff-Parkinson-White syndrome)
VI Reflex vagal stimulation	Often effective by: A Terminating the attack B. Blocking the AV conduction (rare)	Ineffective

should be given with the blood pressure under *continuous control* and the ECG *under constant observation. The injection of 1 Gm should* be given very slowly (at about 0.1 *Gm* every 2 min). If the attack is terminated after only part of the above dosage is given, the administration can be discontinued. The injection should be *interrupted* if the ECG shows *evidence of a definite* increase in the duration of the *QRS* complex or if there is a significant drop in blood pressure. Since several fatalities have been reported following the *intravenous* administration of Pronestyl (generally with rapid administration), the intramuscular *injection is preferred* in several institutions as *being less* dangerous. For this, 0.5 to 1.0 Gm is *injected*, and the injection can be repeated one to *three times* at 1- *to* 4-*hour* intervals until the tachycardia is controlled. If there is no special cause of worry, the oral route can be employed. With *doses* of 0.5 Gm every 2 hr, or 1 Gm every 4 hr, the attack may be terminated within a period varying from hours to days in about 70 per cent of cases (Bellet *et al.*, 1952).

Quinine, quinidine, and Pronestyl are contraindicated in cases where there has been an AV block.

Digitalis favors the formation of ectopic foci in the ventricles. However, it *is occasionally* capable of causing the disappearance of a ventricular tachycardia, *apparently* by improving the circulation, through a prolongation of *the refractory period*, and through a decrease *of conduction* (*Scherf* and Kisch, Gilson and Schemm). Obviously, this drug cannot even be considered if the attack has occurred while the patient is under digitalis therapy or in a prefibrillatory state with *multifocal* ventricular complexes. If this is not the case and heart failure is present or *there is low blood pressure*, digitalis can be used.

Potassium salts, on the contrary, are specifically *indicated in* paroxysmal *ventricular tachycardia favored* by overdigitalization, because *during toxic digitalis action, an intracellular decrease of potassium and magnesium ions occurs*. Under such conditions, an attack can be terminated by the administration of 2 Gm potassium chloride or citrate *every 2 hr or* by the careful intravenous *infusion of an isotonic* potassium *chloride solution*. *Overdosage* should be *prevented by* determination of the serum potassium levels and through observation of the ECG.

Magnesium sulfate is similarly worth a try, particularly in ventricular tachycardia *under* the effect of digitalis (Zwillinger, Boyd and *Scherf; Szekely and Wynne*). As with *premature beats caused* by digitalis, 15 to 20 ml of a 15 to 20 per *cent solution* of magnesium sulfate should be *injected slowly into a vein*.

Morphine has been recommended by Gonzalez Sabathié (*intravenous injection of* 10 to *40 mg*); *papaverine* has been advocated by Elek *and Katz*.

Atropine. Atropine sulfate (*1 to 2 mg*, intravenously or *intramuscularly*), *alone or in combination* with *quinidine, has also* been *successful in some cases* (Salley; Levine, 1945). Atropine is generally administered only when the ventricular rate has already *significantly decreased through the use of quinidine*. Its action seems *based on* a prolongation of the refractory period.

COMPLICATIONS OF THE PAROXYSMAL TACHYCARDIAS

Heart failure can be induced by prolonged attacks *of the rapid forms of tachycardia. This* occurs *particularly* in ventricular tachycardia when the heart has been previously damaged. *Pulmonary edema* (possibly associated with pulmonary infarction) and hepatic engorgement, followed by abdominal distention and ascites, *usually disappear rapidly after the end of the attack, unless* the *previous* cardiac condition *was* too poor. Cardiac glycosides may be necessary but should be administered with caution.

A myocardial infarct may be the *result of a* prolonged paroxysmal tachycardia *in cases* with *coronary stenosis. Precordial* pain can reveal *this occurrence*, *although* such pain may be absent if there is a simultaneous onset of failure. After each prolonged attack of tachycardia, one should examine the temperature, white cell count, blood *pressure*, transaminase activity, sedimentation *rate*, and *ECG*, in order to exclude the *occurrence* of a myocardial infarct.

Electrocardiographic evidence of coronary *insufficiency may* last from *minutes* to hours after the attack is over and *is* present particularly in cases with poor coronary flow *and* ventricular hypertrophy *or other myocardial le-*

lation, the latter to a functional depression of the conducting system. Observations in cases with myocardial infarcts reveal that the ventricular septum is a preferred site from which ventricular tachycardia can be elicited. It is not known how far the histologic changes that produce ventricular tachycardias spread into the periphery.

There is, so far, no anatomic proof of congenital abnormalities in cases of obstinate extrasystolic tachycardias with good prognosis (Parkinson and Papp).

Prognosis. The prognosis of ventricular tachycardia depends primarily upon the underlying cardiac condition. It is severe in patients where the attack is provoked by a *fresh myocardial infarct.* Among 42 such patients of Armbrust and Levine, 28 (or 64 per cent) died within 1 month, 10 lived longer than 2 years, and the longest survival was for 11 years. The outlook has considerably improved with modern therapy, including anticoagulants, treatment of shock, and treatment of the tachycardia itself, *if immediate treatment is given.* Even today, prognosis is severe for patients who have a cardiogenic shock during the attack of tachycardia. The same is true for the ventricular tachycardia during infections, because the attack reveals the existence of myocarditis The outlook is extremely poor if the ventricular tachycardia occurs during an advanced stage of *heart failure.* In younger patients, this is usually due to chronic myocarditis; in older cases, the underlying basis is generally a degenerative process due to coronary heart disease (and often an old infarct). The designation of these types as *terminal* reveals their prognosis According to Strauss, 80 per cent of such patients die within 24 hr, according to Cooke and White (1943), one-half of such patients die within the first 3 weeks and the other half within the next few months, the longest survival being for 18 months. The immediate prognosis is somewhat better if the paroxysmal tachycardia occurs during therapy with digitalis glycosides. Then, discontinuance or modification of therapy can affect the tachycardia. Even so, the outlook remains poor on account of poor myocardial conditions.

In relatively rare cases with *apparently normal hearts,* the prognosis is considerably better, though occasional fatalities during an attack occur even in such cases, apparently through transformation of the ventricular tachycardia into flutter and then fibrillation

Treatment. Certain measures effective in supraventricular tachycardia are also effective in the ventricular form; others, however, fail. Certain medications are specifically indicated in ventricular tachycardia. Since the prognosis becomes worse with prolongation of the attack whenever the heart is damaged, treatment should be instituted immediately.

Reflex vagal stimulation and parasympathomimetic drugs are worthless, as they do not influence a ventricular ectopic focus. In spite of this, carotid sinus pressure should be tried in order to exclude a case of supraventricular tachycardia with an equivocal ECG picture. If unsuccessful, it will confirm the diagnosis of a ventricular form. On the other hand, no time should be lost while trying vagal stimulating drugs.

Quinidine can be tried as in supraventricular tachycardia. If the general conditions are severe, one should not wait for the effect of an oral therapy but should employ, instead, a more rapidly acting intravenous preparation: *quinidine lactate,* 0 6 Gm in 200 ml of 5 per cent glucose at a speed of 2 to 3 ml per min (Kantner), or *quinidine gluconate* or *hydrochloride,* 0.3 to 0.8 Gm in 20 to 100 ml of isotonic saline solution injected through not less than 10 min (Bellet et al., 1949), or a slow injection of *quinidine dihydrochloric carbamide,* 0.3 to 0.5 Gm The heart action should be monitored during these injections, and administration of the drug should be discontinued as soon as the tachycardia is terminated. Quinidine can be given by the intramuscular route, using about twice the above dose and repeating this dose, if necessary, at hourly intervals.

Procaine amide (Procaine amide hydrochloride, *Pronestyl*) has occasionally proved superior to quinidine, even though it has basically the same mode of action. As a result, this drug has become the drug of choice in ventricular tachycardia. When special haste is indicated, i e , if the attack lasted more than 12 hr, a fresh myocardial infarct has occurred, or there is severe congestive failure, Pronestyl can be given intravenously. Since it has a hypotensive action, this method of administration is *not* recommended if the blood pressure is already very low. In all cases, the injection

3

Extrasystoles

DAVID SCHERF

Extrasystoles are contractions of the whole heart or parts of the heart elicited by the preceding beat and therefore bound to it by a fairly constant interval (*constant coupling*). They are often called *premature contractions*. However, in atrial fibrillation, some of the beats conducted from the atrium are more premature than are the extrasystoles. On the other hand, extrasystoles may not be premature when they appear late in diastole and excite only part of the heart while the rest is excited by the normal impulse. The above definition excludes ectopic extra beats caused by automatism of deeper centers (idioventricular or parasystolic beats). The former come late in diastole, the latter appear in all phases of diastole and therefore do not have a fixed coupling.

HISTORICAL REMARKS

The "skipping of the heart beat," caused by an extrasystole, and the intermittent pulse were known to physicians for many centuries. The Chinese discussed them thousands of years ago. With rare exceptions (see Chinese medicine), this phenomenon was considered to have a bad outlook. Only at the very end of the nineteenth century did Cushny and Wenckebach simultaneously discover that the intermittent pulse is in most cases caused by extrasystoles, for the first time they described correctly this arrhythmia in man.

TYPES

Extrasystoles are divided into different groups depending on the part of the heart from which they originate. While under normal conditions, impulses are formed only in the so-called specialized tissue ("specialized fibers") which alone has automaticity or the ability to form impulses (SA node, AV node, bundle of His, bundle branches and ramifications), under abnormal conditions, extrasystoles may originate in the common muscle fibers. One can elicit extrasystoles from any part of the atria or ventricles by local application of aconitine, digitalis, strophanthin, or hypertonic solutions of sodium chloride and barium chloride. The problem is not definitely solved because it is impossible to decide by histologic methods how far the specialized tissue reaches. It seems, however, improbable that the extrasystoles and atrial tachycardias which appear on application of aconitine on the tip of the left atrium could be caused by firing off of impulses in specialized fibers.

COUPLING

The length of the coupling in a given patient varies little, differences usually amounting only to 0.02 to 0.04 sec. Most often the duration of the coupling is around 0.32 sec, but it may be longer, rarely shorter (0.26 sec). Lewis called the coupling "the forced cycle," as it is ended by the forced beat or extrasystole. The duration of the coupling may be influenced by drugs, such as quinidine, or by the appearance of bundle branch block.

VENTRICULAR EXTRASYSTOLES

These are recognized in the electrocardiogram as premature ventricular complexes, usually of abnormal form. Only rarely do these extrasystoles show a ventricular complex of

sions, being more pronounced and more lasting for attacks of long duration.

Emboli in the greater or lesser circulation can occur after a prolonged attack if a cardiac thrombosis has occurred during the tachycardia.

POSTTACHYCARDIAL SYNDROME

The *posttachycardial syndrome* consists of ECG changes of the ST-T segments which follow paroxysmal tachycardia continued for several days, and which persist from a few days up to 8 weeks. The longer the tachycardia has lasted, the more likely it is for these changes to occur, and the longer they will persist. They consist often of pronounced inversion of the T wave in several leads, which usually makes it possible to localize the disturbance in either the left or the right ventricle. The QRS complex is usually not involved (Fig 11-5B–G). The inverted T wave is generally less pointed than in myocardial infarction, the Q-T interval is prolonged initially. This picture is less common after a supraventricular than after a ventricular tachycardia. This supports the idea that the abnormal T waves reveal damage of that ventricle from which the tachycardia had its origin (Gallavardin, Graybiel and White, Cossio et al.). This phenomenon may occur in otherwise normal cases.

The *symptoms* of the patient are overshadowed by lassitude, especially after a prolonged attack. A transient slight cardiac dilatation has been observed (Cossio et al).

The ECG picture may be considered as evidence of fatigue of the ventricular myocardium resulting from the prolonged tachycardia The metabolism is altered by the uneconomical tachycardia—more altered if the myocardium was damaged before the attack

The *evaluation of the ECG* requires great care, and the following points should be considered:

1. The ECG alterations may be considered evidence of a posttachycardial syndrome only if they were *not* present prior to the attack. Ventricular tachycardia may mask the pattern of an abnormal ECG.

2. If the attack was associated with precordial pain, or if heart failure followed it, one should consider the possibility that there has been a *myocardial infarct.* The clinical data may help in the differential diagnosis, although their absence does not rule out a small infarct. Changes of the QRS complex that were not present before the attack, or the onset of a monophasic wave with elevation of the S-T interval in certain leads, speak for a *fresh myocardial infarct.*

3. If the inversion of the T wave is found chiefly in the chest leads V_1 to V_3, one should consider *acute cor pulmonale* (pulmonary infarct caused by embolism).

4. If the attack was treated with large doses of digitalis glycosides, the typical "digitalis effect" of the ECG is to be expected Quinidine or Pronestyl may cause flattening of the T waves, possibly associated with broader U waves, and occasionally with a prolongation of the QRS complex.

Little is known still about the *pathologic anatomy* of the posttachycardial syndrome. At autopsy of one case, moderate hypertrophy and dilatation of the heart were found, without any other evidence of myocardial lesions (Cossio et al)

In general the *prognosis* is good Even so, occasionally, and without any apparent particular reason, a fatality may occur during an attack.

The abnormal *metabolic* state of the heart requires physical rest and good nutrition Since the nature of this metabolic disturbance has not been clarified, more definite therapeutic measures cannot be used However, adequate supply of glucose, potassium, vitamins, and possibly metabolic enzymes is indicated; there is no indication for cardiac glycosides.

normal systole (Fig. 11-7G). The next normal beat following the extrasystole is not disturbed and comes at the exact moment it would have come had there been no extrasystole (*compensatory pause*).

An interesting phenomenon has been seen in diseased hearts: the T wave of the first postextrasystolic beat may be abnormal, becoming flat or even inverted, particularly in leads V_3 or V_4

Under abnormal conditions, particularly in elderly patients, the first postextrasystolic beat is an "escaped" idioventricular beat from a deeper ventricular center (Figs. 11-7B, 11-9B).

If every beat of the basic rhythm is followed by an extrasystole, there is a *bigeminal rhythm;* if two extrasystoles follow each normal beat, a *trigeminy* is present A succession of many extrasystoles (Fig 11-7D, E) may also be called a *paroxysmal tachycardia.*

Even if extrasystoles continue to occur for many years, they show in the most minute detail the same electrocardiographic pattern, as long as the heart remains healthy and they originate in the same focus If the extrasystoles are *polifocal* or *multiform* (Fig 11-7C, D and 11-9B), they are definitely significant They originate in several foci and spread over the heart in different patterns When several centers exist, one may conclude that several abnormally functioning fibers are present, therefore, *multiform extrasystoles indicate heart disease* They are seen in the different forms of *myocarditis* and most frequently in coronary heart disease (Fig 11-9B)

One should be aware, however, that extrasystoles may be the consequence of *digitalis* action, regardless of how small a dose the patient may be getting They may appear even after a single dose of 0 3 Gm standardized powdered leaves of digitalis After digitalis is discontinued, they may persist for 2 to 3 weeks On the other hand, they were absent in several instances of suicide with digitalis Experimental and clinical data indicate that they appear in digitalized hearts that are exhausted or damaged and *in which the potassium content of the muscle is diminished* The appearance of multiform ventricular extrasystoles during the administration of digitalis is a phenomenon of great importance, as most of these patients develop more and more extrasystoles if digitalis is continued, ultimately, ventricular tachycardia may appear with alternating or continuously changing ventricular complexes Such tachycardias may also appear spontaneously in patients with damaged myocardium (Fig 11-7E).

ATRIAL EXTRASYSTOLES

Extrasystoles originating in the atria are recognized in the electrocardiogram by the appearance of *premature P waves* which, in most instances, have a different form than in the existing sinus beats They may be inverted, higher or shorter, differently slurred, or notched. Because of their prematurity, these P waves are often hidden in the preceding T waves and may be recognized only by the change of form of the T waves. In continuous bigeminy, every T wave contains a P wave, so that there is no possibility of comparing them with normally shaped T waves; the diagnosis is then difficult (Fig. 11-8B). Too often, in the absence of a clear P wave, the diagnosis of an AV extrasystole is made and it is presumed that the atrium and ventricle contract simultaneously. Atrial extrasystoles on their way down to the ventricles may find the path blocked by refractory tissue from the preceding systole, and therefore will not be followed by a ventricular contraction. These are called *blocked atrial extrasystoles* (Fig. 11-8C); often, for the same reason, the spread of the atrial extrasystole is abnormal within the ventricles (*aberrant atrial extrasystoles*). This happens even in healthy hearts and has no special significance (Fig. 11-8C). Atrial extrasystoles are followed by *a pause which usually is noncompensatory*

If atrial extrasystoles are *multiform*, atrial fibrillation usually follows, such abnormalities are often seen in the elderly patient and are an indication for therapy with quinidine

EXTRASYSTOLES FROM THE BUNDLE OF HIS

These extrasystoles are rare (Fig 11-7A). They are characterized by premature ventricular contractions showing the same ventricular complexes as the existing sinus rhythm.

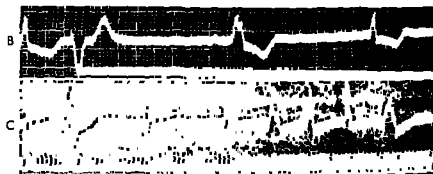
SINOATRIAL NODE EXTRASYSTOLES

These extrasystoles are also rare, but they have been studied experimentally and a few typical instances have been observed in man. They are characterized by *premature P waves* exhibiting the same form as the P waves of

the same form as the normal complexes; this is the case only when they originate in the bundle, above the bifurcation (Fig. 11-7A). In most instances the QRS complexes and T waves are abnormal, because *the stimulus originates* in one of the *ventricles* and consequently spreads abnormally. The QRS complexes may be widened, slurred, and notched; the T waves are often oppositely directed (Fig. 11-7B, D) Sometimes, particularly when the basic rhythm is slow, an extrasystole is sandwiched between two sinus beats without disturbing the existing rhythm; this is called an *interpolated extrasystole* (Fig 11-7F). Usually, however, at some time during the extrasystolic contraction, the next normal atrial contraction occurs but cannot be conducted to the ventricles because of the refractoriness caused by the extrasystolic contraction. Thus an extrasystole replaces, so to speak, a

A

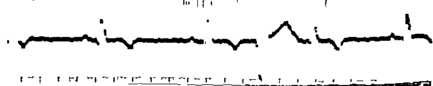
B



C

D

E



G

Fig. 11-7. A. Lead III. Prolonged P-R interval in a patient with left bundle branch block; a ventricular extrasystole arises above the bifurcation of the AV conduction system. B. Lead III. Atrial fibrillation, digitalis effect, and ventricular extrasystole, followed by an ectopic, idioventricular, automatic beat. C. Lead III. Atrial fibrillation with multiform ventricular extrasystoles. D. Lead III. Complete AV block; an automatic beat is followed by a series of ventricular extrasystoles which are multiform. E. Lead III. Groups of ventricular extrasystoles with alternation of form. No digitalis had been given. In the vast majority of the cases, such an arrhythmia is the consequence of administration of digitalis. F. Lead III. Interpolated ventricular extrasystole in a patient with posterior infarction. G. Lead I Ventricular extrasystole. The normal P wave is visible between the QRS complex and the T wave of the extrasys

are excited simultaneously, in this case the P wave is hidden in the QRS complex. In another form, the premature P wave precedes the QRS complex by an interval which is *shorter* than the normal P-R interval of the patient. These P waves are very low and positive in lead I, peaked, of short duration, and deeply inverted in leads II and III; they are positive in aVR and inverted in aVF In a third form, the abnormal P wave appears after the QRS complex, usually between the QRS complex and the T wave (Fig. 11-8A).

With certain, well-studied exceptions, the first-named form originates *in the middle part* of the AV node, the next one *in the upper (atrial) part*, and the last one in the *lower (ventricular) portion* It seems that premature inverted P waves with a normal P-R interval may originate in the so-called *coronary sinus node*, an extension of the AV node to the orifice of the coronary sinus For one or several beats following atrial extrasystoles, the P waves of the regular rhythm may show an abnormal form (Fig 11-8D); there is so far no satisfactory explanation for this phenomenon, which is not rare

RETURN EXTRASYSTOLES

These rare extrasystoles may be subdivided into several forms One of them has been well analyzed experimentally but has not been observed in clinical cases. If ventricular extrasystoles are initiated by any method in the dog, they often are conducted backwards into the atria (*retrograde conduction*) If the last of a series of extrasystoles reaches the atria, it is followed by a beat of normal form, and analysis shows that the extrasystolic impulse, while on its way to the atria, has *returned to the ventricles* In another form of the same phenomenon also observed in man, *return extrasystoles* are seen in the type of AV rhythm in which the P wave is present between the QRS complex and the T wave Thus in Fig 11-8E, obtained in an experiment in a dog, all beats with such P waves are followed by a return extrasystole Since one cannot assume that the part of the AV system above the bifurcation which had just conducted the impulse to the atria is able to conduct it immediately down again to the ventricles, one must assume a longitudinal dissociation of the AV system permitting retrograde conduction in one part, normal conduction in another.

EXTRASYSTOLES DUE TO DRUGS AND DIFFERENT COMPOUNDS

Extrasystoles are frequently the consequence of drug action. They may appear sometimes in dangerous numbers and may lead to fatal ventricular fibrillation The most important compounds are listed below.

Digitalis extrasystoles have been mentioned above; it may be stressed again that in the healthy person and in most patients with abnormal hearts such extrasystoles do not appear even after administration of large doses. They appear in experimental animals only before death but are easily elicited if digitalis or strophanthin is applied locally to the cardiac surface (Fig. 11-9A). They are particularly common in the hypertrophied and dilated hearts of rheumatic mitral lesions or coronary sclerosis; investigations have demonstrated a diminished content of potassium in the muscle fibers of these hearts.

Digitalis extrasystoles frequently show differences of form, which may be only slight or very marked.

Quinine, quinidine, and Pronestyl are known to elicit extrasystoles and dangerous tachycardias, as well as fibrillation, in man and in the experimental animal. Their use in combination with certain anesthetics is dangerous

Chloroform and cyclopropane both cause extrasystoles of varying form. The appearance of extrasystoles in anesthesia with cyclopropane is less dangerous than with chloroform. Why cyclopropane occasionally leads to so many extrasystoles and why they do not occur in other cases, is unknown *Trichloroethylene* has a similar action

Epinephrine, caffeine, and *nicotine* often elicit extrasystoles.

CLINICAL DATA

Incidence. Extrasystoles are common in the healthy person. They appear so often that the statement has been made that no adult escapes them permanently. In most people, they are asymptomatic. Extrasystoles appear in all ages and have been often heard on auscultation of the fetal heart. It is not decided as yet whether atrial or ventricular extrasystoles are more common, but in early youth, the atrial type seems to predominate.

Different statistics compiled on different material (hospital patients, patients with heart

the existing sinus beats; often, but not invariably, they are followed by a pause which is *shorter* than that necessary to create a normal P-R interval. The rarity of these extrasystoles and of those from the bundle of His and the AV node is understandable if the following law is considered: centers with highly developed automaticity, i.e., with the ability to form impulses, rarely show abnormal beats of the extrasystolic type; however, centers in the peripheral ramification of the nodes or in the Purkinje system more often exhibit their abnormal extrasystolic impulses.

ATRIOVENTRICULAR (NODAL) EXTRASYSTOLES

These extrasystoles may be divided into three groups. In one, the atria and ventricles

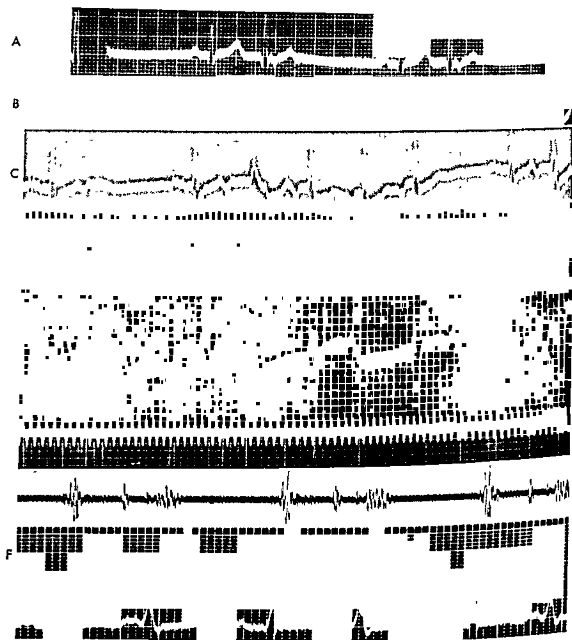


Fig. 11-8. A Lead I. *Nodal or ventricular (?) extrasystoles* with retrograde conduction to the atria, with an inverted P wave between the QRS complex and the T wave B *Atrial extrasystoles in bigeminal groups* with alternation of duration of coupling, and aberration of the QRS complexes of those extrasystoles which have a shorter coupling C. *Blocked atrial extrasystole* at the beginning of the tracing; later, four extrasystoles, with the first conducted to the ventricles with delay and aberration. D *Atrial extrasystoles* with abnormal P wave of the first postextrasystolic beat. E. *AV rhythm* in a dog; lead III. All those beats with an inverted P wave between QRS complex and T wave are followed by a *return extrasystole*. F. Phonocardiogram and lead II of a patient with *bigeminy*. The extrasystole creates only a 1st sound; the 2d sound of the extrasystolic beat is absent.

are excited simultaneously, in this case the P wave is hidden in the QRS complex. In another form, the premature P wave precedes *the QRS* complex by an *interval* which is *shorter* than the normal P-R interval of the patient. These P waves are very low and positive in lead I; peaked, of short duration, and deeply inverted in leads II and III, they are *positive* in aVR and inverted in aVF. In a third form, the abnormal P wave appears after the QRS complex, usually between the QRS complex and the T wave (Fig. 11-8A).

With certain, well-studied exceptions, the first-named form originates in *the middle part* of the AV node, the next one in *the upper (atrial) part*, and the last one in the *lower (ventricular) portion* It seems that premature inverted P waves with a normal P-R interval may originate in the so-called *coronary sinus node*, an extension of the AV node to the orifice of the coronary sinus For one or several beats following atrial extrasystoles, the P waves of the *regular rhythm may show an* abnormal form (Fig. 11-8D), there is *so* far no satisfactory explanation for this phenomenon, *which is not rare.*

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EXTRASYSTOLES DUE TO DRUGS AND DIFFERENT COMPOUNDS

Extrasystoles are frequently the consequence of drug action. They may appear some*times* in dangerous numbers and may lead to fatal *ventricular fibrillation*. The *most important compounds* are listed below.

Digitalis extrasystoles have been mentioned above, it may be stressed again that in *the* healthy person and in most patients with ab*normal* hearts such extrasystoles *do not appear* even after administration of large doses. They appear in experimental animals only before death but are easily elicited if *digitalis or strophanthin is applied* locally to the cardiac surface (Fig. 11-9A). They are particularly common in the hypertrophied and dilated hearts of rheumatic mitral lesions or coronary sclerosis, *investigations have demonstrated a* diminished content of potassium *in the muscle* fibers of these hearts.

Digitalis extrasystoles *frequently* show differences of *form, which may* be only slight or very marked

Quinine, quinidine, and Pronestyl are known to elicit extrasystoles and dangerous tachycardias, *as well as fibrillation, in* man and in the experimental *animal. Their use in com*bination with certain anesthetics is dangerous.

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Epinephrine, caffeine, and *nicotine* often elicit extrasystoles.

CLINICAL DATA

Incidence. Extrasystoles are common in the healthy person. They appear so often that *the statement* has been made that no adult *escapes* them permanently In most ...

...ation of the fetal heart. It is *not* decided as yet whether *atrial* or ventricular *extrasystoles* are more common, *but in* early youth, the *atrial type* seems to *predominate.*

Different *statistics* compiled on *different* material (*hospital* patients, patients with heart

disease, patients in private practice) show an incidence of 1.5 to 3 8 per cent.

Factors and Diseases Eliciting Extrasystoles. Extrasystoles may appear *after exercise*. In the majority of such instances, the extrasystoles indicate the presence of myocardial or coronary disease. Actually, the appearance of extrasystoles (usually of varying shape) following exercise should arouse the suspicion of *coronary sclerosis*. Extrasystoles after exercise have been seen in *myocarditis*, and in diphtheria.

Extrasystoles are influenced by *posture*. They are more often found in the supine patient or may be seen only if a patient lies on the left or right side.

They appear in some patients during constipation, menstruation, pregnancy, or with meteorism, in others, after smoking or on sexual excitement. Extrasystoles are common in acute myocardial infarction and in cardiac aneurysms In the former, they seem to originate in the area of reactive inflammation surrounding the infarction. They require therapy with quinidine because of the danger of fibrillation. While extrasystoles are common in diphtheritic myocardial necrosis, they occur less frequently in active rheumatic fever, in spite of the frequent involvement of the myocardium, including the specialized tissue.

Extrasystoles are common in the preexcitation syndrome and in a variety of allergic conditions. They are rare in hyperthyroidism in spite of the frequent occurrence of fibrillation.

Symptoms. As mentioned above, symptoms are present only in a small minority of individuals with extrasystoles, but in some unfortunate ones, the symptoms may be distressing.

Many patients complain of *palpitation*. Only further questioning reveals that this sensation consists in a sudden jumping, skipping, or somersault of the heart, and is not continuous but may repeat itself several times per minute. Interpolated extrasystoles may be more dis-

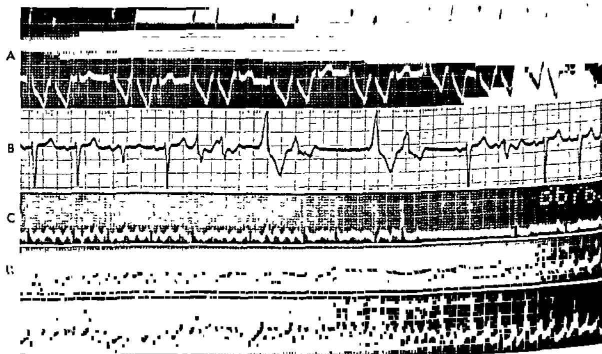


Fig. 11-9. A Lead III in a dog *Trigeminy and multiple extrasystoles* created by focal application of digitoxin to the conus of the right ventricle. B Lead III *Multiple and multiform ventricular extrasystoles and abnormal automatic ectopic beats* in a 72-year-old patient who had received digitalis C. End of an attack of *atrial fibrillation* in a 65-year-old man D Dog, lead II *Atrial flutter* elicited by focal application of aconitine on the tip of the appendix of the right atrium. Cooling of the area of application abolished the flutter and made the sinus rhythm reappear. Discontinuation of the cooling led to reappearance of flutter These results, readily reproduced and confirmed, could not be explained if a circus movement were present. E *Atrial flutter*, elicited in a dog by application of aconitine, is transformed into fibrillation whenever the right appendix is stretched.

tressing than the usual ones It is typical for these sensations to come mostly at rest, which is the time extrasystoles most often occur, chiefly on account of slower rate.

Other patients complain of *dizziness or even of fainting* Questioning elicits that this dizziness lasts only "a second" The reason for the vertigo in the absence of a long cardiac standstill is not known

Pain is a not infrequent complaint It may be "knifelike" or stabbing, and its brevity alone speaks against coronary involvement. Often it is not the *extrasystole itself which* causes palpitation or pain but the first postextrasystolic beat with its larger stroke volume.

Some patients with extrasystoles have a most interesting *cough reflex*. The cough appears simultaneously with the extrasystoles, comes from "nowhere," and may be very annoying The mechanism is not clear, but the *presence of a reflex from the heart or the* pressoreceptors to the respiratory *tract is obvious*

All these sensations are aggravated if the patient feels his pulse and finds it intermittent

Signs. Most extrasystoles are diagnosed by auscultation; the heart tones of the premature contraction followed by a pause are heard However, without an electrocardiogram mistakes, although rare, can occur, since dissociation with interference, parasystole, or even a periodically dropped beat may lead to a similar auscultatory impression The 1st sound of the extrasystolic contraction is often accentuated, the 2d sound may be absent (Fig 11-8F)

The pulse "skips," as it does in periodically dropped beats, in bigeminy, the extrasystoles may be so premature that their pulse waves are not transmitted to the periphery because of the small output this is the "pseudobradycardia" of our forefathers

Extrasystoles may also give the impression of a gallop rhythm, since the two sounds of the beat preceding the extrasystole are occasionally followed by the only sound produced by the extrasystole

PROGNOSIS

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…n over a period of years, they do not lead to complications and can be ignored On the other hand, extrasystoles can elicit fibrillation and, if the ventricles are involved, *sudden death. This happens when extrasystoles occur extremely early, during the last few hundredths of a second* of the T wave of the preceding beat (Fig. 11-12C). If a premature impulse reaches the heart during this phase, the so-called *critical or vulnerable phase*, it leads to rapid firing of impulses resulting in multiple extrasystoles, flutter, or fibrillation. *This does not happen under normal conditions but occurs when the heart is in an "abnormal metabolic" state, for instance when there is abnormal excitability* of a center because of lack of potassium or calcium This is why extrasystoles during chloroform anesthesia and those in acute myocardial infarctions bring so great a potential risk.

THERAPY

When extrasystoles appear, a thorough examination is indicated. If the patient is not aware of the existence of the arrhythmia, it is best not to mention it If he becomes aware of it, he is often disturbed, since for the layman an irregularity of the pulse seems to herald the threat of a cardiac catastrophe. Reassurance and explanation of the phenomenon may help *in many cases It may* be of value to point out to the patient that *no restriction of* activity is required and that he may lead a normal life

The treatment with drugs is reserved for those patients discussed above in whom the extrasystoles create some risk and for those who complain that the arrhythmia disturbs them The *treatment of choice* is *quinidine*, which is given three to six times daily in the form of tablets containing 0 2 Gm, after a test dose of 0 2 Gm Most extrasystoles, but by far not all, disappear with this medication If hypersensitivity prevents the use of quinidine, *one may use Pronestyl*, 0 75 Gm (three capsules), three *to four* times daily While ventricular extrasystoles *respond* well, the atrial type is less frequently influenced

The administration of 4 to 8 Gm daily of *potassium chloride* helps, particularly in digitalis-induced extrasystoles, but this therapy is to be used only if renal function is normal, because it carries the danger of other disturbing arrhythmias. Digitalis therapy often abolishes extrasystoles not caused by this medica-

disease, patients in private practice) show an incidence of 1.5 to 3.8 per cent.

Factors and Diseases Eliciting Extrasystoles. Extrasystoles may appear *after exercise.* In the majority of such instances, the extrasystoles indicate the presence of myocardial or coronary disease. Actually, the appearance of extrasystoles (usually of varying shape) following exercise should arouse the suspicion of *coronary sclerosis.* Extrasystoles after exercise have been seen in *myocarditis,* and in diphtheria.

Extrasystoles are influenced by *posture.* They are more often found in the supine patient or may be seen only if a patient lies on the left or right side.

They appear in some patients during constipation, menstruation, pregnancy, or with meteorism, in others, after smoking or on sexual excitement Extrasystoles are common in acute myocardial infarction and in cardiac aneurysms In the former, they seem to originate in the area of reactive inflammation surrounding the infarction. They require therapy with quinidine because of the danger of fibrillation. While extrasystoles are common in diphtheritic myocardial necrosis, they occur less frequently in active rheumatic fever, in spite of the frequent involvement of the myocardium, including the specialized tissue

Extrasystoles are common in the preexcitation syndrome and in a variety of allergic conditions. They are rare in hyperthyroidism in spite of the frequent occurrence of fibrillation.

Symptoms. As mentioned above, symptoms are present only in a small minority of individuals with extrasystoles, but in some unfortunate ones, the symptoms may be distressing

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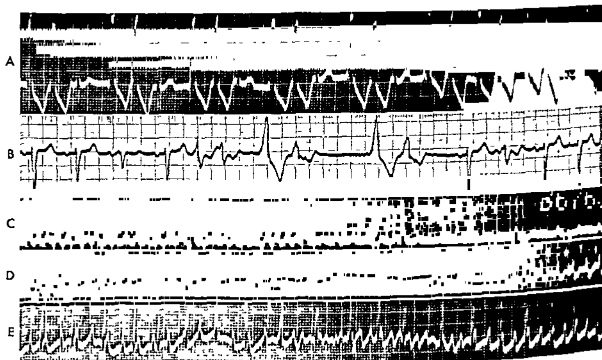


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The pulse "skips," as it does in periodically dropped beats, in bigeminy, the extrasystoles may be *so premature that* their pulse waves are not transmitted to the periphery because of the small output: this is the "pseudobradycardia" of our forefathers

Extrasystoles may also give the impression of a gallop rhythm, since the two sounds of the beat preceding the extrasystole are occasionally followed by the only sound produced by the extrasystole

PROGNOSIS

The vast majority of extrasystoles represent a harmless phenomenon Whether they appear singly or in series, occasionally or continuously, even over a period of years, they do not lead to complications and can be ignored. On the *other* hand, extrasystoles can elicit fibrillation and, if the ventricles are involved, sudden death. This happens when extrasystoles occur extremely early, during the last few hundredths of a second of the T wave of the preceding beat (Fig. 11-12C). If a premature impulse reaches the heart during this phase, the so-called *critical or vulnerable phase*, it leads to rapid firing of impulses resulting in multiple extrasystoles, flutter, or fibrillation. *This does* not happen under normal conditions but occurs when the heart is in an "abnormal metabolic" state, for instance when there is abnormal excitability of a center because of lack of potassium or calcium This is why extrasystoles during *chloroform anesthesia and those in acute myocardial infarctions bring so great a* potential risk.

THERAPY

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The *treatment with drugs is reserved for* those patients discussed above *in whom the* extrasystoles create some risk and for those who complain that the arrhythmia disturbs them The treatment of choice is *quinidine*, which is given three to six times daily in the form of tablets containing 0.2 Gm, after a test dose *of* 0 2 Gm. Most extrasystoles, but by far not all, disappear with this medication. If hypersensitivity prevents the use of *quinidine*, one may use *Pronestyl*, 0 75 Gm (three capsules), three to four times daily. While ventricular extrasystoles respond well, the atrial type is less frequently influenced.

The administration of 4 to 8 Gm daily of *potassium chloride helps*, particularly in digitalis-induced extrasystoles, *but this* therapy is to be used only if renal function *is normal*, because it carries the danger of other disturbing arrhythmias Digitalis therapy often abolishes extrasystoles not caused by this medica-

tion, but one would not give digitalis for such a harmless phenomenon.

MECHANISM

The mode of origin of extrasystoles is known only for the "return" extrasystoles, where one may assume that the impulse conducted in a retrograde way from the ventricles or the AV node to the atria *returns* and "reenters" the ventricles. For the others, the mechanism remains unknown.

There are two main theories. They have in common the assumption that the beat preceding the extrasystole elicits it. The constant coupling of the extrasystoles and the many experiments showing that they disappear when the eliciting beat is inhibited by vagal stimulation prove this assumption to be correct.

One theory, which exists in numerous modifications, assumes *a reentry movement;* it is believed that the impulse, while spreading over the heart, is conducted in a penultimate twig of the conduction system only in one direction with some delay, and that the conduction path is then reentered, thus a second impulse, the extrasystole, spreads over the heart. It must be conceded that these theories are purely theoretical and are not based on experimental facts or clinical observations. There is only one experimental finding, by Schmitt and Erlanger, which is often quoted in support of this theory. The authors believed they had shown that in a small muscle strip, an impulse starting at one end reached the other and then returned to the initial point The authors assumed that the impulse was conducted only in one part of the cross section of the strip (from A to B) so that it could return to A via another pathway. Experiments by Arvanitaki and Bozler have, however, shown that this assumption is incorrect. The impulse traveling from A to B may elicit in one cell at B a repeated firing of impulses and, when a cell becomes depolarized more than once, the second depolarization may spread again over the muscle strip and reach A.

This leads to a second explanation which the author favors· that the *extrasystoles are due to the repeated firing off of impulses.* Normally, when an impulse spreads over the heart, every cell is depolarized once When, because of prolonged negative afterpotential, loss of calcium, or other abnormalities, one cell becomes depolarized *twice* (afterdischarge), a bigeminy appears, since the second depolarization, appearing after the refractory phase of the heart, may form a propagated impulse. A similar phenomenon has been demonstrated for various types of nerves, and its occurrence was proved in the heart muscle of experimental animals If a long series of depolarizations follows (*repetitive response*), the patient has one of several forms of paroxysmal or ectopic tachycardia.

4

Flutter and fibrillation

DAVID SCHERF

ATRIAL FORM

Definitions. In atrial flutter, the atrium contracts 200 to 400 times per minute, the movements are coordinated and are named after the rapid movements of the wings of certain birds (Fig. 11-9D). In atrial fibrillation, the impulses formed in the heart are more rapid, so that as they spread over the atria, they meet refractory tissue and coordinated contraction ceases (Fig. 11-9C). A fibrillating atrium gives the impression of the rippling seen when a gentle evening breeze agitates the surface of a lake. Occasionally the atrial contractions are slightly irregular, so that they cannot be called flutter, while they are not sufficiently irregular for fibrillation. A status of *impure flutter* or *flutter-fibrillation* is then said to exist.

BRIEF HISTORICAL REMARKS

Fibrillation was first elicited experimentally over 150 years ago, but the "pulsus irregularis perpetuus," the "delirium cordis," was known for a long time to occur in man. That atrial fibrillation is responsible for this common clinical phenomenon was proved for the first time simultaneously by Rothberger and Winterberg (1909) and by Sir Thomas Lewis (1909). Flutter was observed and so named by Williams (1887) but described in man by Jollie and Ritchie (1910).

THE ELECTROCARDIOGRAM

The electrocardiographic picture is easily recognized in atrial fibrillation. Instead of normal P waves preceding the QRS complexes, irregularly formed fibrillation waves (F waves), with a rate up to 600, are present. They continuously vary in form and rate (Fig. 11-9C). The ventricular activity is completely irregular, except in those patients who also have complete AV block. The F waves are sometimes coarse, sometimes fine, and may even be invisible in most leads, with the exception of V_1 and V_2. However, the absence of P waves and the complete irregularity of the heart make the diagnosis possible in the last case.

In atrial flutter, the P waves or F waves are regular in form (Fig. 11-10B). They follow each other like the regular teeth of a saw with continuous motion, but short isoelectric lines may separate one F wave from another (Fig. 11-9D). It should be stressed that the form of the F waves alone differentiates flutter from fibrillation: these waves are regular in flutter and irregular in fibrillation (Fig. 11-11).

The ventricular rate and rhythm in flutter show all possible variations. The ventricles may beat rapidly and regularly at a rate greater than 300 per minute when every atrial impulse is conducted to the ventricles (*flutter with full rhythm*). If an intraventricular conduction disturbance coexists or if, because of the rapid rate, the intraventricular conduction is aberrant, a picture similar to that of a ventricular tachycardia appears in the electrocardiogram (Fig. 11-10F). More often the arrhythmia is confused with an atrial paroxysmal tachycardia (Fig. 11-10C). However, in the majority of cases, the AV conduction system is able to conduct only every second, third, or fourth atrial impulse to the ventricles, so that a 2:1, a 3:1, or 4:1 block appears (Fig. 11-10B). If the blocking is irregular, the ven-

tricles may show the same *complete arrhythmia* as in fibrillation. If there are 4:1 and 2:1 blocks alternating regularly, a *bigeminal rhythm* caused by extrasystoles may be diagnosed on auscultation.

CLINICAL DIAGNOSIS

This is easy in *fibrillation* because of the complete irregularity of the heart. Confusion with irregularly placed extrasystoles may occur and is fatal if the series of irregularly grouped ventricular extrasystoles seen in digitalis intoxication is confused with atrial fibrillation with a rapid ventricular rate, and if the physician, without the help of an ECG, decides that the patient needs more digitalis. In doubtful cases one may be aided by the knowledge that extrasystoles usually disappear after exercise or the inhalation of amyl nitrite while the irregularity of fibrillation increases with these measures

The clinical diagnosis of *atrial flutter* is possible in most instances. A fundamental clinical rule should be that every regular heart activity with a rate of 100 to 160 per minute should arouse suspicion of flutter with 2:1 or 3:1 block. In sinus tachycardia, the rate increases with the patient standing or performing moderate exercise, and gradually returns to its former level with rest. In flutter, as well as in the paroxysmal tachycardias, the rate remains the same. However, more strenuous exercise causes change of block, so that a 3:1 block changes into a 2:1, or the latter into full rhythm, there are characteristic mathematic relations between the rate prior to and after

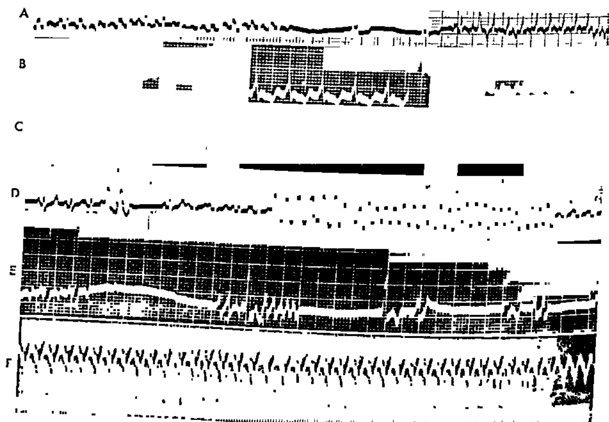


Fig. 11-10. A *Atrial flutter*, caused in a dog by focal application of aconitine, is immediately abolished by cooling the area of application Two sinus beats appear. Discontinuation of the cooling leads immediately to atrial fibrillation B The three standard leads. *Atrial flutter* with 2 1 block. C The three standard leads. *Atrial flutter* with complete AV conduction; these tracings are readily confused with paroxysmal atrial tachycardia D. *Paroxysmal ventricular flutter* appearing during cooling of a small area of the right ventricle of a dog E. *Sinus standstill* and short attacks of *atrial flutter* immediately following focal application of acetylcholine on a dog's atrium. F. Lead III of a man with *paroxysmal tachycardia*; further analysis of many tracings, taken over a period of weeks, revealed that the condition under investigation was *atrial flutter* and *aberrant intraventricular conduction.*

the exercise. The original rate is suddenly restored after a few minutes Carotid pressure or any other vagal reflex stops a paroxysmal tachycardia for a longer or shorter time but affects the rate in flutter or sinus tachycardia only while pressure is exerted.

Whether it is permissible to differentiate atrial flutter from paroxysmal tachycardia has been questioned, particularly since rapid firing of impulses is considered to be the responsible mechanism in both conditions *The author believes that these conditions should be separated in spite of certain similarities.* In paroxysmal tachycardias, carotid pressure often abolishes the tachycardia In flutter, this does not happen and actually vagus stimulation increases the flutter rate and causes fibrillation (Fig 11-12B) Many drugs which are effective in abolishing atrial tachycardias are useless in flutter. Atrial flutter is common in cardiac patients and rare in otherwise apparently healthy individuals; the situation is reversed for paroxysmal tachycardias Flutter often changes, spontaneously or after digitalis administration, into fibrillation This is extremely rare in a paroxysmal tachycardia.

CLINICAL CONSEQUENCES

The *ventricular rate* alone is of importance in these abnormal rhythms If with a higher degree of block, the rate is around 80, the patient has an almost normal circulation and may not even notice the restoration of normal rhythm With a rate of about 120, the patient will be handicapped, particularly on undertaking physical exertion With higher rates, cardiac failure, with high venous pressure, hepatic enlargement, fall of the arterial pressure, and cardiac enlargement, will result in direct relation to the rate.

OCCURRENCE

Atrial fibrillation (a more common event) and atrial flutter may occur in apparently healthy people. They may be observed for decades or even during a lifetime without other evidence of cardiac involvement. It is possible that a postinfectious (streptococcic) myocarditis, subclinical and rapidly healed, was originally responsible. We knew one physician who had been refused life insurance because of atrial fibrillation when he was in his twenties; he died at 84, and not from heart disease. The fibrillation never stopped and never required therapy since the ventricular rate remained slow.

In certain lesions, fibrillation is common. It appears sooner or later in most patients with mitral stenosis, hyperthyroidism (which is often masked), or coronary sclerosis. It is rare in cor pulmonale and in many congenital heart lesions. It has been described in healthy young men after severe physical strain. It occurs under certain experimental conditions when the atria are stretched or overfilled (Fig. 11-9E) A high vagus tonus (Fig. 11-12A) and the topical application or intravenous injection of acetylcholine cause flutter or fibrillation (Fig. 11-10E) in the experimental animal. Fibrillation is occasionally seen in a normal dog when the vagus in the neck is stimulated with a faradic current (Fig. 11-12A).

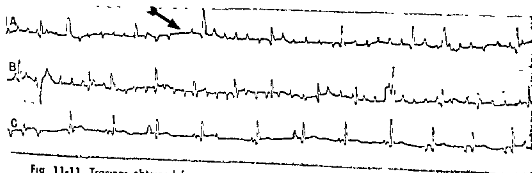


Fig 11-11 Tracings obtained from a patient with shifting of the pacemaker from the SA node to the AV node (C) There is also a change from positive to negative P waves during the presence of flutter This is also explained by two active centers, one in the SA node and one in the AV node, at times, when both centers form impulses simultaneously (arrow in A), an almost isoelectric P wave is obtained.

THERAPY

Fibrillation. It has been stressed that the ventricular rate alone is responsible for the disturbances caused by flutter and fibrillation. Actually, in fibrillation the atria do not contribute to cardiac dynamics as they are practically paralyzed, and with the disappearance of sinus rhythm, venous and atrial pressures rise, even when the ventricular rate during fibrillation was slow. This does not hold true, however, for all patients, and it must be stressed that fibrillation may persist for many decades without the patient's being handicapped in any way, provided the ventricular rate is slow.

The chief therapeutic problem is to slow down the ventricular rate, and this is often accomplished by *digitalis*. This is, however, a purely symptomatic form of therapy Patients respond to it readily unless complications such as hyperthyroidism, active rheumatic fever, or pulmonary embolism exist. Once the ventricular rate is below 80 beats per minute, a maintenance dose will keep it at this level.

Only rarely should an attempt be made to eliminate fibrillation. This is recommended when hyperthyroidism is cured but fibrillation persists; if fibrillation appears during pneumonia or some other infectious disease and does not disappear spontaneously; or when fibrillation has just started in slight mitral stenosis and a loud presystolic murmur indicated earlier that the left atrium still contributed to ventricular filling. In the vast majority of cases defibrillation is not indicated. Several independent investigators have found that *quinidine* therapy causes death in 4 per cent of the cases, even when doses of not more than 1.5 to 2 0 Gm are given daily. The

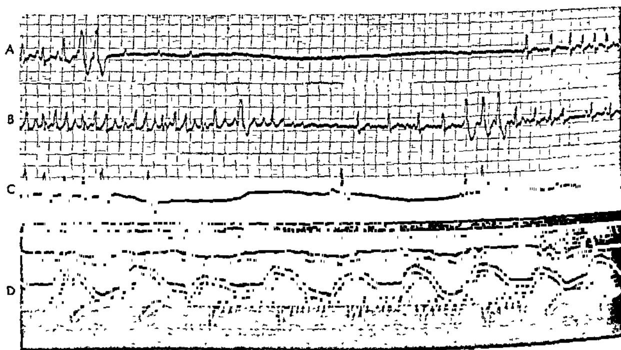


Fig. 11-12. A and B are continuous Lead III, dog experiment. The animal had received veratrine before, and parts of the SA node had been crushed by a clamp. In A, atrial fibrillation appears during faradic stimulation of the right vagus nerve in the neck. When this fibrillation changed into flutter, a repetition of the vagus stimulaton led immediately to fibrillation. Sinus rhythm reappeared on termination of the second vagus stimulation C Dog experiment; veratrine, applied locally to a small area of the outflow tract of the right ventricle, had led to the appearance of ventricular extrasystoles. Cooling of the area of application led to the disappearance of the extrasystoles. There is cardiac standstill, presumably because the rapid extrasystoles were retrogradely conducted to the atria and inhibited the SA node. The first sinus beat is followed by an atrial extrasystole, which, reaching the ventricle during its critical, or vulnerable, phase, elicits ventricular fibrillation. D. Dog experiment. Lead from anus to esophagus. Complete AV block existed after severing both bundle branches The top line represents a signal, the second a mechanogram of the right atrium, and the third a mechanogram of the right ventricle. One short electrical shock (signal) leads to a short attack of atrial fibrillation.

incidence of fatalities increases if larger doses are administered. Patients have *died from ventricular fibrillation or respiratory standstill or* systemic embolism. Thus, the patient is exposed to *a not inconsiderable* danger without too great a benefit. *In most* patients with mitral *stenosis*, *the* dilated left *atrium* fails anyway to *contribute to the dynamics of the circulation*. In any case this therapy should *always be carried* out only in a hospital, for *continuous supervision of the patient is essential*. The *second* chief reason against this therapy *is that, in* most patients (actually in *almost* all of them if they suffer from rheumatic heart disease or coronary sclerosis), fibrillation *reappears and often is again* present within a few days after therapy is discontinued. In order to avoid embolism, it is recommended that an anticoagulant be given for 14 days prior to the quinidine therapy, so that thrombi already *present* will have time to adhere to the wall and no new ones will form.

Experience shows that with any method of administration of *quinidine*, one succeeds in reestablishing sinus rhythm in about 60 per cent of the patients. At first, a test dose of 0.2 Gm is given in order to determine whether there is hypersensitivity. *On the next day*, 0.2 Gm is given every 2 hr from 8 A.M. to 8 P.M., or 0.4 Gm every 4 hr day and night. The success is the same with both procedures. If no result is obtained, the single doses may be increased, but this is recommended only under close supervision, since the risks are increased. In recent years, frequent use of quinidine therapy for interruption of fibrillation has been recommended without good reasons.

Flutter. In this condition, treatment is usually required and is more difficult. It is more often necessary because only exceptionally does the patient with flutter have a slow ventricular rate at rest and with the ordinary exertions of daily life. The rate is usually too high and the circulation deteriorates. The therapy is more difficult, since in most cases the administration of digitalis in the usual dosage does not inhibit AV conduction and cannot thereby slow the ventricular rate. The slower impulses of flutter are less inhibited on their way to the ventricle than the faster impulses of fibrillation.

Since flutter is transformed *into fibrillation by large doses of digitalis*, one can prescribe *from the beginning* about 0.5 mg *digitoxin* daily, and *in most* patients will succeed within *a few days* in transforming the flutter into *fibrillation*. When this is accomplished, the continuous administration of small maintenance doses of digitalis will keep the rate down; sometimes fibrillation changes spontaneously *into sinus rhythm*. *Some* authors prefer to start with *quinidine* at once without using digitalis, the dosage being the same as in *atrial* fibrillation. If quinidine is used in flutter or fibrillation, a paradoxic *phenomenon is common*, viz., an increase of *ventricular rate*. *This* is explained by the atropine-like action of quinidine on the vagus endings, which appears even with the use of ordinary clinical doses. *There* are, *however*, *instances of atrial* flutter *in which digitalis therapy* does not change the existing rhythm, despite the largest tolerated doses, and in which quinidine also fails. In such cases one must abandon treatment and try again after a few months.

VENTRICULAR FLUTTER AND FIBRILLATION

Ventricular flutter has been described repeatedly, but no accepted rules exist on its separation *from* rapid ventricular paroxysmal tachycardia (Fig. 11-10D). As in atrial flutter, the rate may be decisive. It may, in the dog, reach 500 or more.

Ventricular fibrillation is one of the most common causes of sudden death, for the circulation stops (Fig. 11-12C). It *is often survived* in the cat and in small mammals, since in them it stops spontaneously. This happens only rarely in man. It has been seen in complete heart block *in* coronary sclerosis, particularly when quinidine is being given. Ventricular fibrillation is a not uncommon cause for fatal accidents during administration *of anesthesia*, particularly with *refrigeration* of the heart.

Of interest *is* the *ventricular fibrillation* which *appears after prolonged hyperventilation* with resulting hypocapnia. *A rise* in serum potassium and a fall *of potassium in* the heart *muscle seem to be responsible*. Two methods are available *to eliminate it* and to revive a patient with ventricular fibrillation. One is the old method of Prevost and Bacelli, who recommended strong electrical shocks. Through the *efforts of Zoll* (1952), relatively simple de-

vices are now available for this purpose and permit stimulation of the heart even with an unopened chest. The other method is rapid exposure of the heart by a large incision in the fourth intercostal space; intracardiac administration of procaine; massage, and administration of oxygen. The latter is done by intratracheal tube or mouth-to-mouth breathing if no tube is available, for quick action is urgent; the cortical centers are very sensitive to lack of oxygen and are damaged if the circulation is arrested for more than 3 min.

Mechanism of Origin. The mechanism of flutter and fibrillation in the atria or ventricles has long been unknown, but recently additional data have been brought forward favoring one of the existing theories. For more than 65 years flutter and fibrillation were explained by rapid impulse formation in one or several centers in the atria or ventricles respectively. There are many modifications of this theory based on experimental evidence. The centers were located in the SA node, in the AV node, or both. These theories were practically abandoned when the *circus movement* theory was developed, mainly by Lewis (1916) and Garrey. Lewis based his work on previous experiments by Mines and Romanes and assumed that a "circus" or "reentry" wave moves up or down the SA node and follows a circular pathway, from this "mother" or "central" wave, the rest of the heart is excited by centrifugal excitation waves. This fascinating theory was generally accepted, and even in textbooks of physiology it was "the" explanation; in some it still is. This was mainly because of the very elaborate and well-arranged experiments of Lewis, which seemed to be convincing. Objections to his theory were raised many years ago but were disregarded. Thus, Rothberger pointed out (1922) that the two fundamental experiments, one in the dog and one in man, which Lewis considered crucial in proving the existence of a circus movement, were actually open to serious criticism Even the existence of a circular path in this area still lacks anatomic proof, and the use of the whole path by a circus wave has never been demonstrated. If this wave were present, broad ligatures across the path should stop electrically induced flutter, but they do not, as demonstrated by the author (1928).

Lewis himself stressed that his theory cannot explain ventricular fibrillation and that this constituted a serious weakness because of the identity of the atrial and the ventricular form. Ventricular fibrillation was explained by Garrey's hypothesis, which is based on much less experimental data than the theory of Lewis.

Experiments of the author and his coworkers have shown that atrial (Figs. 11-9D and 11-10A) and ventricular flutter and fibrillation (Fig. 11-10A) can be caused by topical application of *aconitine*. Other experiments demonstrated that atrial flutter can, in this way, be caused by rapid impulse formation in one center; that atrial fibrillation can be evoked by rapid impulse formation in one or several centers, that ventricular flutter can originate from rapid firing of impulses in one center. There is no proof of the mechanism of ventricular fibrillation, but the activity of several centers is probable. It is assumed, on the basis of experimental data, that rapid impulse formation in one center induces rapid impulse formation in others, as this relationship has been known for a long time to exist in the nervous system.

Since the existence of at least two forms of fibrillation of the atria causing identical electrocardiographic patterns has been proved, viz., the arrhythmia arising in one or in several centers, other forms may exist. There is, however, no proof that a "circus movement" may be responsible, if it occurs locally, it may well be merely the consequence of rapid impulse formation and the appearance of islands of refractory tissue. If this is the case, it would be maintained by fibrillation but would not sustain it.

5

Pathologic findings in disturbances of rate or rhythm

ANTONIO COSTA

SINUS BRADYCARDIA

A possible cause of sinus bradycardia is *arteriosclerosis* of the artery which supplies the SA node (Fiorio), followed by fibrosis of the nodal tissue Caution should be taken in the evaluation of the pattern, because similar lesions have been considered responsible for paroxysmal tachycardia (*Doerr*). A *congenital* absence of the SA node has never been observed, *even in malformations* of the superior vena cava Theoretically, this would cause a slow pulse due to nodal rhythm.

ATRIAL FIBRILLATION

It is difficult to find a correlation between atrial fibrillation and atrial lesions of rheumatic, sclerotic, or toxic nature On the contrary, it is more likely that, in accordance with Prinzmetal's concept (1951), there is an ectopic focus, generally in the posterior wall of the right atrium, represented by an area of intact myocardium within the rest of the degenerated tissue

ATRIOVENTRICULAR BLOCK AND BUNDLE BRANCH BLOCK

The *pathologic findings in cases with disturbances* of conduction are by no means concordant According to Bach, Pardee, Laubry, etc , the electrocardiographic pattern of block can be found in patients in whom histologic sections fail to disclose lesions of the conducting bundles This possibility, however, is denied by others (Beretta and Maestrelli), who found alterations in all the cases submitted to study Even in the so-called "functional blocks," structural lesions of the conduction system should be admitted, in addition to functional disturbances (Fig 11-13). Several authors, on the other hand, deny that a localized or diffuse damage of the cardiac muscle can determine a pattern of bundle branch block without simultaneous lesions of the conducting system (Scherf, 1925, Laubry et al., Smith, 1932, Robinson).

Transient or *functional block* is often due to minor lesions of the branches that may escape *even an accurate study On the other hand,* diffuse degenerative or sclerotic lesions of the *AV node and bundle of His have been* described without the occurrence of specific electrocardiographic pattern of block

According to Monckeberg, failure to demonstrate lesions of the bundle of His in typical cases of block may be explained by (1) incomplete histologic examination of the conducting system, (2) lesions of the neurologic components of the bundles, (3) existence of anatomic abnormalities, such as anastomoses between the two branches

The value of a *functional factor* was overestimated in the past but still should not be *altogether disregarded.* A lesion of a small area of the conducting system may become "functionally" total *because of compression* and stretching of the other fibers Serial histologic studies have shown *an interruption of the*

branches in all cases of block clinically diagnosed

The localization of the lesion in cases of bundle branch block has been the object of numerous studies, because for a long time, there was no agreement between the findings and the ECG pattern. In most observations, the alterations involved both branches, even though one of them was generally more injured than the other. However, the reversal of opinion due to the school of Wilson finally reconciled the clinical interpretation with the pathologic findings. On the whole, few cases of bundle branch block have been studied histologically and the technique used is not always above reproach Mahaim (1928) emphasized the need for serial, uninterrupted sections of the bundle of His and its branches. His conclusions were as follows:

1 In bundle branch block, the lesions are usually bilateral, even though one of the branches shows more severe damage

2. The branch with the worst lesions is usually that which had been suspected on the basis of electrocardiography.

3. Right bundle branch block is most often due to a lesion of subdivisions of the anterior descending branch of the left coronary artery.

4 Left bundle branch block, as a rule, is not caused by ischemic factors because of its dual blood supply. It is usually caused by an inflammatory process which spreads from the valves to the septum and from there to the left branch. These conclusions are not completely above criticism but give an idea of the complexity of the problem.

It is interesting to mention that extensive lesions of both branches have been found without typical ECG patterns of bundle branch block (Yater, 1938). This might be explained by the existence of a few intact fibers, still able to conduct the stimulus. Therefore, it shall be concluded that the most important point is the localization of the lesion and not its nature

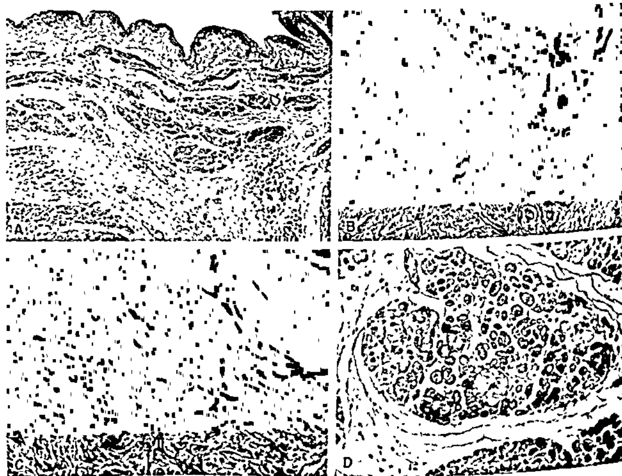


Fig. 11-13. A Rheumatic myocarditis Aschoff nodes near the left branch of the AV bundle. B SA node; moderate hyperplasia of the connective tissue C. SA nodes; severe hyperplasia of the connective tissue. D. Right branch of the bundle of His. degenerative phenomena of the conducting fibers.

Vascular, inflammatory, and degenerative lesions may affect the conducting system either with the rest of the myocardium or as an isolated process (Fig. 11-14). The *vascular changes* are characterized by *small hemorrhagic areas* favored by the rich vascularization, and by areas of degeneration. AV block or bundle branch block has been often observed in the course of a myocardial infarct Mahaim (1928) and Hochrein have described the frequency and causes of this condition

In general, it is admitted that the bundle branch block which appears in cases with coronary arteriosclerosis is due to lesions of either one or both of the branches According to Mahaim, the occlusion of the anterior descending branch causes *right bundle branch block* or *AV block* Actually, the AV node, the bundle of His, and its right branch receive their blood supply from this arterial branch On the contrary, left bundle branch block appears when the right coronary artery is also occluded Many authors (among them Hochrein) have accepted this viewpoint, which is not accepted by Master and coworkers

Among the *inflammatory processes*, acute interstitial myocarditis, rheumatic nodules, and purulent myocarditis have been described Small abscesses of the conduction bundle should be considered as a result of diffusion of the inflammatory processes to the bundle through the endocardium, less often they are caused by a shower of mycotic emboli, as in a case of Mahaim.

AV block is an important complication of diphtheria and reveals the existence of severe myocarditis.

Generally, the AV block, which is frequently observed in *many infectious processes* (pneumonia, scarlet fever, influenza, mumps, rubeola), is not accompanied by specific lesions of the conducting system; the block is likely to be caused chiefly by action of toxins on the AV node and the conducting bundles. Such a toxic-infectious process may explain the AV block observed in the course of *rheumatic fever* and *diphtheria* without focal lesions [1] In some of these cases, albuminoid, hyaline, fatty,



Fig. 11-14. A SA node, hyperplasia of the elastic tissue in the wall of the nodal artery. B. Thickening of the wall of the nodal artery in a patient with pentalogy of Fallot. C. Left branch of the bundle of His, isolated fibers of the conductive system surrounded by thick fibrotic tissue.

waxy, or vacuolar degeneration has been observed

Specific granulomatous processes have been observed in addition to more common inflammatory lesions, these processes were particularly described in cases of *syphilitic* or *tubercular myocarditis*

Syphilis is an uncommon cause of AV block. However, the conduction disturbance may be due to a gumma infiltrating the bundle of His or both branches, to gummatous myocarditis spreading from the aorta, or to an aortitis causing narrowing of the coronary mouths.

In cases of *calcific aortic stenosis*, different

[1] A toxic process may be such as to be inapparent upon routine histologic examination while it might be revealed by more refined studies of histochemistry. *Editor.*

degrees of AV block may be caused by the spreading of the calcific process from the aortic ring to the conduction tissues in the ventricular septum.

Fiorio and Marino studied the alterations of the AV system in *experimental thyrotoxicosis*, and observed degenerative lesions consisting of sclerosis and calcification of the system, with its partial or total interruption. Less frequently were noted atrophic phenomena caused by compression of calcium deposits at the level of the trigoni fibrosi.

Primitive and secondary tumors may cause the interruption of the conducting system (Mahaim, 1928). Nagayo described a primary leiomyoma of the branches, and Monckeberg, a lymphangioendothelioma of the AV node. *Fetal and neonatal fibroelastosis* may cause interruption of the bundle of His and its branches (Mahaim, 1928).

Congenital AV block is considered by Yater and coworkers as due to a septal defect or to a defect in the development of the conductive tissue. Histologic studies have shown in some cases a separation between the AV node and the bundle of His caused by a fibrous nucleus. This lesion is, however, very rare.

In a study on the conducting system in congenital heart diseases, Costa and Fiorio observed that the defects of the septum membranaceum have little importance in regard to the disposition and structure of the adjoining conduction system. Defects of the interventricular septum, on the other hand, are often associated with disturbed growth of the bundle of His resulting in poor development and abnormal course of the left branch.

THE WOLFF-PARKINSON-WHITE SYNDROME

The Wolff-Parkinson-White syndrome is apparently caused by an abnormal and specific lesion in the atrium or near the AV node, the hypothesis of an aberrant bundle has never been documented by serial histologic studies[2] Katz, in one-half the cases with this syndrome, observed the existence of heart disease of either inflammatory (rheumatic, syphilitic, etc.) or degenerative type

The most common pathologic findings are interstitial edema, vacuolar degeneration of the myocardial fibers, chronic rheumatic myocarditis, and scars near the AV node.

[2] Good evidence in favor of an aberrant bundle has been gathered, including histologic studies (Chap 10). *Editor.*

6

Sinoatrial and atrioventricular blocks

SAMUEL BELLET

SINOATRIAL BLOCK

General Features. In sinoatrial (*SA*) block, there occurs a sudden decrease in the heart rate, usually to almost half the previous normal rate, which may last for one cycle, several cycles, minutes, or hours. This decrease in heart rate can be explained on the basis of an actual physiologic block occurring within or around the structure of the SA node and preventing conduction of the impulse to the atria.

This sudden halving of the heart rate is usually preceded by a slight speeding up of the heart and is followed by cycles which are slightly longer but which then gradually shorten until the usual cycle is reestablished. Both the atria and ventricles participate in the irregularity (Fig. 11-15). The heart rate may be as slow as 30 to 36 beats a minute. This condition should be differentiated from other types of slow heart action, particularly sinus bradycardia and various degrees of AV block.

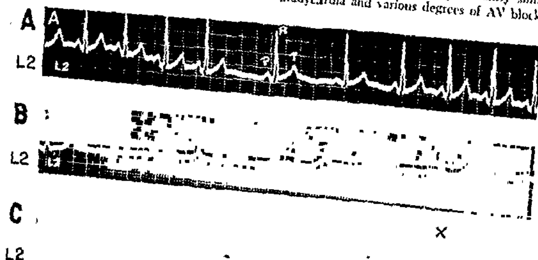


Fig 11-15 A Sinus arrhythmia. Note the phasic variation of the R-R interval. The rate increases during inspiration and becomes slower during expiration. The shorter cycles are associated with a decreased T-P interval. The P-R interval remains constant throughout. B. Sinus bradycardia. Both the atrial and ventricular rates are slow (34 per minute), and the P-R interval is normal. C. Note the presence of a normal sinus rhythm with a rate of 75 per minute. In the last cycle (marked X) a long pause is observed. The cycle length of the long cycle is slightly less than that of two normal cycles. This constitutes a SA block (occasionally the R-R interval of the long cycle is exactly equal to that of two normal cycles).

degrees of AV block may be caused by the spreading of the calcific process from the aortic ring to the conduction tissues in the ventricular septum.

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The most common pathologic findings are interstitial edema, vacuolar degeneration of the myocardial fibers, chronic rheumatic myocarditis, and scars near the AV node.

[2] Good evidence in favor of an aberrant bundle has been gathered, including histologic studies (Chap. 10). *Editor.*

heart; *dizziness* and *faintness* may occur if the sinus pauses are prolonged.

Diagnosis. The diagnosis of SA block may be suspected clinically but can best be made by means of the electrocardiogram.

Electrocardiogram. In the electrocardiogram, there is a pause or series of pauses, each one of which is slightly less than double the normal P-P interval, *occasionally, the pause is exactly equal to that of two normal cycles.* Both the atrial and the accompanying ventricular complexes are lost during the pauses (Fig 11-16) The duration of the SA block may vary as follows. (1) the irregularity may be observed for a few cycles, (2) the rate may be suddenly halved, dropping, for example, from 75 to 38 per minute—this slow rate may persist for several minutes or longer, (3) the disturbance may be present for long periods of time and may be the underlying mechanism for long-continued bradycardia

Because SA and AV block are due to somewhat similar factors, it is not surprising that these two irregularities are frequently associated

Treatment. No treatment is required in the absence of symptoms or signs. However, when the sinus rate drops to a low figure with the resultant production of syncopal attacks (more common in the older age group), it is advisable to administer certain drugs to diminish or eliminate vagal tone, e g , Isuprel, 10 mg, sublingually, ephedrine sulfate, ⅜ gr (25 mg) three times a day, or other sympathomimetic drugs or atropine sulfate, or Banthine Drugs which would increase vagal tone, such as Prostigmine or digitalis, should be omitted or used with caution Toxicity due to quinidine, procaine amide, or potassium, which may be an additional causative factor, should be appropriately treated

PROLONGED SINUS PAUSES (CARDIAC STANDSTILL) AND ATRIOVENTRICULAR NODAL ESCAPE

If, for any reason, the SA node fails to initiate the cardiac impulse, the AV node, because it also possesses the property of rhythmicity to a degree only slightly below that of the SA node, soon "escapes" and initiates the heart beat It maintains a slow and regular rhythm until the SA node can again resume its function as the pacemaker. Ordinarily, the AV node is prompt to assume its pacemaker function In certain instances, however, this assumption may be delayed, with the result that there is complete cardiac standstill. This asystolic state may be of sufficient duration to produce dizziness or even syncopal attacks. Such pauses are the result of vagal effects which may occur spontaneously as a result of reflex disturbances or may be produced in susceptible individuals by carotid sinus pressure. These seizures usually respond to atropine or ephedrine If the AV node fails to take over the role of pacemaker, a ventricular center, usually located in the upper portion of the interventricular septum, may assume this role. This phenomenon is called "ventricular escape" If the periods of cardiac standstill are unduly prolonged because of failure of the AV node or an idioventricular center to assume temporarily the role of pacemaker, cardiac arrest or ventricular fibrillation ensues. Such episodes are particularly apt to occur as the result of depression of the conducting tissue by anesthesia, hypoxia, potassium, or full doses of quinidine or procaine amide.

WANDERING PACEMAKER BETWEEN THE SINOATRIAL AND ATRIOVENTRICULAR NODES

Under conditions of increased vagal tone, the rhythmicity of the SA node becomes reduced and that of the AV node remains the same or increases somewhat. Consequently, the function of the pacemaker shifts to the AV node. With a subsequent decrease in vagal tone, the pacemaker returns to the SA node. As seen on the electrocardiogram, this shift is not sudden but occurs over a space of several beats Progressive changes are seen in the P waves during the shift They undergo change in size, shape, and direction simultaneously, with a shortening of the P-R interval until the classic "high nodal" pattern is achieved (inverted P wave with a P-R interval of less than 0.10 sec) With a return of the pacemaker to the SA node, these changes occur in reverse. At times, P waves, transitional in form, are observed They are thought to be due to the simultaneous firing of the SA and AV nodes. Since the shift of pacemaker function is not abrupt, there must be a phase in which each node has partial pacemaker activity, and thus two impulses traverse the atrial muscle in op-

Etiology. SA block is observed as a normal finding in individuals presenting an increased vagal tone. By itself, it is not considered abnormal. It may be produced in a susceptible individual by carotid sinus pressure. It is also observed in infectious states, during acute rheumatic carditis, in the presence of arteriosclerotic processes involving the SA node, and as a result of digitalis. Quinidine, procaine amide, and hyperpotassemia may also produce this condition; however, these drugs tend to depress atrial contraction relatively early without concomitant effects on the ventricles; thus, they produce AV dissociation and ultimately sinus arrest with the maintenance of ventricular beats.

Pathology. No characteristic pathologic findings are observed in SA block. It may occur in patients with disease of the SA node due to rheumatic carditis or degenerative conditions, it may follow occlusion of the right coronary artery, which supplies the SA node in 60 per cent of hearts. Occasionally, an arteriosclerotic process present in the region of the carotid sinus may tend to produce SA block by its increase of vagal tone.

Symptoms. No symptoms are usually observed with SA block. This arrhythmia may, however, produce symptoms under the following circumstances. Occasionally, the period of block may be prolonged to several seconds, resulting in syncopal attacks However, the periods of cardiac standstill are frequently shortened by the temporary assumption of the role of pacemaker by the AV node (*nodal escape*) or by a ventricular focus (*ventricular escape*). Such episodes may result in a sensation of palpitation or forceful beating of the

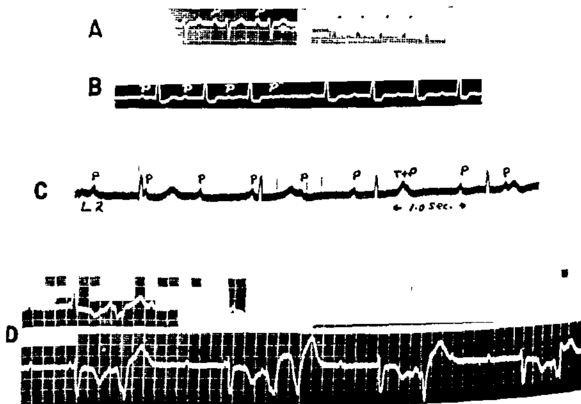


Fig. 11-16. A Partial AV block. Initial strip shows prolongation of the P-R interval, which measures 0.22 sec. Second strip. note the P-R interval prolongation with the tachycardia (ventricular rate, 150 per minute). Note that the P wave of the prolonged P-R interval immediately follows the preceding QRS complex, coming between the QRS complex and the T wave. This P wave controls the following QRS complex. B Partial AV block. Progressive increase in the prolongation of the P-R interval until a dropped ventricular beat is observed at P_X (Wenckebach phenomenon). C. Complete AV block. The atrial rate is 100, the ventricular rate is 37 per minute. Each pacemaker is beating independently of the other. D. Complete AV block with ventricular extrasystoles, some of which appear in groups of two in succession Note the regular atrial rate of 88 per minute and a regular but slow ventricular rate (16 per minute) in most cycles, the two rhythms are entirely independent of each other.

should lead one to suspect the diagnosis (see Chap. 7).

In partial block (2:1), exercise or amyl nitrite may abruptly double the *ventricular rate.* When the *apical rate is regular and ranges from 20 to 40 per minute* and is relatively *unaffected by exercise or atropine,* complete AV block should be suspected. The 1st *heart* sound [illegible] AV

[illegible]

relatively loud; when *they are far* apart, the 1st *sound is faint* (*see also* Chap. 8). The independent movements of *the atria* are usually visible upon a fluorescent screen.

The auscultatory phenomena in AV block should be differentiated from premature systoles, *SA* block, sinus arrhythmia, sinus bradycardia, and AV *nodal rhythm.* A 3:2 AV block *may simulate a* bigeminal rhythm The diagnosis is clearly established by the electrocardiogram.

ELECTROCARDIOGRAM. Partial AV block is recognized easily by the electrocardiogram, *which clearly shows regularly* recurring, normally shaped P waves with prolonged P-R intervals (Fig 11-16) *The* P-R *interval is* prolonged to over 0.21 sec in adults *and over* 0 18 sec in children With a higher grade of partial block, dropped beats may be detected However, prolongation of the P-R interval or nonconducted atrial impulses of other etiologies *must* be excluded. Thus, in atrial premature systoles and *in the atrial* beat *occurring at the* time of the nodal escape, prolonged P-R intervals, nonconducted atrial impulses, or both, may be observed AV dissociation and interference dissociation may also be associated with P-R interval prolongation not due to partial AV block (*see* Chap 11) In all these instances, the atrial *impulse* reaches the AV junctional tissue during its normal relative or absolute refractory phase In AV block, on the other hand, the cause for the disturbance resides in a depression of the AV junctional tissue

Complete Atrioventricular Block. In complete AV block, the atria beat *regularly* at a *rate of* 70 to 80 per minute in response to their pacemaker, the SA node, and the *ventricles* also beat regularly at a rate of 20 to 40 *per minute* in response to their center located in the lower portion of the AV node, in the bundle of His, or *in the upper portion* of the interventricular septum. These *two pacemakers function entirely independently of each other. The atrial* rate is influenced by the vagus and by factors which influence sympathetic tone. With normal sinus rhythm, the ventricular rate is controlled entirely by the events occurring in the atria In complete *AV block,* this situation no longer holds true since the ventricles presumably have no vagal innervation, *therefore, they* usually are not influenced *by changes* in vagal tone. The *ventricular rate,* however, can vary *to some slight degree,* being modified by factors that alter sympathetic tone, such as fever and the injection of epinephrine or other sympathomimetic drugs. If the idioventricular pacemaker is located in the lower portion of the *AV node, terminal* fibers of the vagus may partially control it. In such cases, a *large dose of atropine may slightly* increase *the ventricular rate*

ELECTROCARDIOGRAM. The electrocardiographic diagnosis is easily made (Fig 11-16). The ventricular complexes occur regularly and slowly. While the ventricular rate is usually slow, 30 to 40 per minute, it may be higher *(60 per minute) in complete heart block due* to digitalis; in the cycles immediately following emergence *from Stokes-Adams* seizures, it may be 100 per minute. The atrial complexes usually occur regularly at a normal rate. Occasionally, the atrial rate is quite rapid, 110 to 150 per minute; rarely it is slow, below 40 per *minute. Occasionally, sequences are observed* where two atrial beats are followed by one *ventricular complex,* thus resembling a 2:1 heart block *The Stokes-Adams syndrome* is characterized by syncopal *attacks,* convulsions, or epileptiform seizures, and occurs *when there* is a period of anoxia lasting over 3 to 9 *sec* These episodes are the *chief hazard* and usual cause of death in patients with complete AV *heart block. The following* are the underlying *mechanisms recorded* electrocardiographically during the *seizures* (Fig. 11-17): (1) a prefibrillatory type of *ventricular tachycardia* (ventricular flutter), (2) ventricular fibrillation, (3) standstill of the whole heart, *(4) ventricular* standstill with maintenance of atrial beating *These mechanisms may* occur either singly or in *various* combinations.

TREATMENT. *Complete Atrioventricular Heart Block* No specific therapy *is* indicated

posite directions, giving rise to the isoelectric or transitional P wave. Such beats are said to be *fusion beats.*

ATRIOVENTRICULAR BLOCK

Partial Atrioventricular Block. Atrioventricular (AV) block may be divided into two types: partial, or incomplete, and complete. AV block may be *temporary, intermittent,* or *permanent,* and one type may develop into the other. The first stage of AV heart block is said to occur when the AV conduction time (P-R interval) exceeds 0.20 sec As the degree of block increases, the AV conduction time becomes longer and longer until dropped beats occur, i e., the ventricles fail to respond to some atrial beats. In a still higher grade of block, there may be observed 2:1, 3:1, or an even higher degree of partial AV block As the block further increases, a stage is reached in which the ventricles fail to respond to *any* atrial impulse, with the result that ventricles and atria beat entirely independently of each other When this stage is reached, the degree of AV block is said to be *complete*

Sudden death may occur during the transition from partial to complete block because of ventricular standstill or ventricular fibrillation.

Clinical heart block has been observed as the result of the following. (1) infections, (2) certain drugs, especially digitalis and, to a lesser degree, quinidine and Pronestyl; (3) congenital cardiac anomalies, (4) vagal stimulation; (5) degenerative conditions; and (6) hypoxia. A discussion of these conditions follows

PATHOLOGY. Coronary artery disease, acute or chronic, is the most common cause of AV block in the older age group. The right coronary artery supplies the AV node in 92 per cent of hearts, the left coronary in 8 per cent Gummata occurring in the AV node or bundle of His are rare (see also Chap. 5)

SYMPTOMS AND SIGNS In partial AV block, no symptoms due to the block itself may be observed, even with a slow ventricular rate The symptoms are those of the underlying disease. Some patients with complete AV block present no symptoms, usually, however, they complain of fatigue on exertion, occasional precordial pain, and consciousness of a vigorous, slow, forceful heart action. These patients usually cannot engage in strenuous physical exertion but generally do fairly well on a reduced physical regimen.

As a result of the slow rate, alterations in the cardiovascular dynamics appear. The cardiac output per beat is increased, but the cardiac output per minute, as compared to the normal, may be decreased in some patients. In complete AV block, because of the fixed cardiac rate, the mechanism for increasing cardiac output in response to exertion and excitement is seriously impaired. Exertion may lead to the production of an extrasystolic arrhythmia and, if continued, may precipitate a Stokes-Adams attack. The systolic blood pressure is elevated, rising to about 170 to 200 mm; the diastolic pressure is usually low, 80 to 100 mm. It is distinguished from true hypertension by the relatively low diastolic pressure resulting from the longer emptying time available to the large arteries between heart beats. The systolic pressure rise is evidence of the enhanced vigor of the slow beats resulting from the greater filling time allowed the heart. The heart, particularly the left ventricle, is enlarged

The important symptoms to be considered in the higher grades of partial and complete AV heart block are the development of *giddiness, fainting,* and *temporary loss of consciousness, with or without convulsive seizures (Stokes-Adams syndrome).* These manifestations of cerebral hypoxia occur during the transition from partial to complete AV heart block, as well as during the course of complete cessation of cerebral flow for 3 to 9 sec or longer.

DIAGNOSIS. The possibility of AV block should be suspected in the presence of any of the conditions mentioned above, especially rheumatic fever, coronary diseases, digitalis, toxic factors, etc. Suggestive evidence consists in a *diminished intensity of the 1st heart sound,* which may be marked. In the presence of dropped beats, the auscultatory phenomena closely resemble and should be differentiated from extrasystoles with a compensatory pause. When there is a delay in AV conduction (prolonged P-R interval) with a regular rhythm ranging from 50 to 80 per minute, the diagnosis is practically impossible by auscultation alone. With rates below 50 or 40 per minute, the possibility of partial or complete heart block should be considered. The presence of a jugular pulse more rapid than that of the apex

1 to 2 hr, depending on desired results, or may be given as a 1:1,000 solution in oil (1.0 ml intramuscularly).

3. *Isuprel* may be given sublingually in doses of 10 to 20 mg every 2 hr or as required, subcutaneously 0.2 mg every 6 hr or as indicated, or intravenously as a continuous infusion of 1 mg Isuprel dissolved in 200 ml of 5 per cent glucose in distilled water, or 4 μg per ml, at a rate of 9 to 20 drops per minute.

4. Molar sodium lactate is effective when given promptly, preferably within 1 to 2 min after the onset of the attack. Initially, it should be given intravenously by syringe in doses of 20 to 40 ml in 1 to 2 min during the attack; then, the solution should be administered as an intravenous infusion at the rate of 60 to 150 drops per minute, the exact rate and amount depending on the effects observed. As the ventricular rate increases, the infusion should be slowed; when it becomes apparent that the pacemaker is spontaneously maintaining a satisfactory rate and the episodes of cardiac arrest have been eliminated, the infusion should be stopped.

5. An *artificial pacemaker* will restore cardiac beating during cardiac arrest. Its use may be lifesaving (see Chap. 12).

6. Because these seizures are so often repeated, thoracotomy accompanied by cardiac massage should be used only when all other methods fail.

7. *Barium chloride* increases the rhythmicity of the cardiac pacemaker but is not frequently used because of its toxic effects.

8. Quinidine and procaine amide have been used in the past when the Stokes-Adams seizures were associated with ventricular extrasystoles, ventricular tachycardia, or ventricular flutter. The administration of these drugs is considered to be contraindicated because they depress cardiac pacemakers.

9. Digitalis in the presence of congestive failure should be used with caution because of its effect in increasing cardiac irritability. AV block, if complete, is not a contraindication to the use of digitalis. Incomplete AV block, on the other hand, might be transformed into complete block by digitalis.

10. Defibrillation may be accomplished by application of the *defibrillator* (see Chap. 12) to the closed chest or after thoracotomy to the exposed heart.

for the *asymptomatic* type of AV block; these patients do fairly well with a slow rate, which may range from 30 to 40 per minute. In the *symptomatic* type of AV block, in which the patient experiences frequent fainting episodes, administration of one or more of the following drugs is indicated: (1) sympathomimetic drugs (ephedrine, Isuprel), (2) oral molar sodium lactate.

Stokes-Adams Seizures. Prophylaxis consists of avoiding those factors which tend to precipitate attacks; e g., strenuous exertion and emotional upsets. Between attacks, measures as described for AV block may be used. The active measures during an attack consist of the following:

1. Direct vigorous thumping on the precordium.

2. *Epinephrine* by intracardiac injection (0 25 to 1 ml of a 1:1,000 solution). This may also be given by slow-drip intravenously, but not more than 0.25 mg should be given by this route, and the drug must be administered at a very slow rate. To prevent repeated attacks, epinephrine may be given in doses of 0.2 to 0.3 ml subcutaneously every

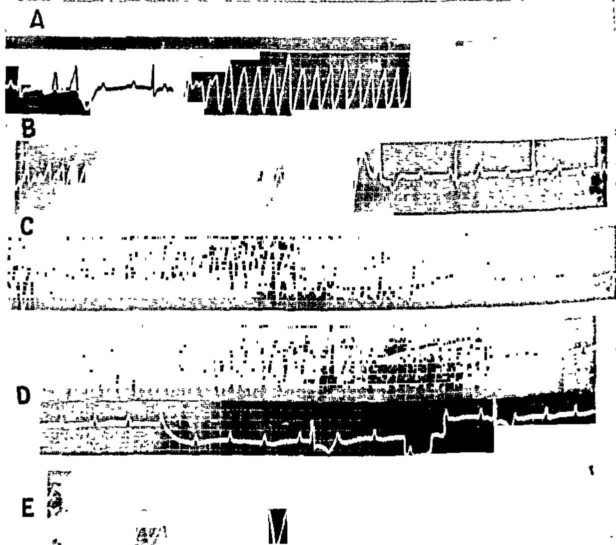


Fig. 11-17. Cardiac mechanisms during a Stokes-Adams attack. Strips A, B, C, D, and E are taken from the same patient, who had a complete AV block A. Paroxysm of *ventricular flutter* with a ventricular rate which averages about 200 per minute Note the markedly aberrant type of ventricular complexes. The end of the strip shows the resumption of the *complete AV heart block* B. Ventricular flutter with a rate of about 200 per minute, terminating in *ventricular standstill*. The atrial rate is maintained at 100 per minute. C. Emergence from an attack of *ventricular standstill*, with the appearance of occasional idioventricular beats. D, and E. *Ventricular fibrillation*. Note the markedly aberrant type of ventricular response. The patient recovered from this paroxysm but succumbed during a subsequent attack.

arteries nearer the heart but not in those more distant When failure is severe, a high pulse wave may be followed by gradually smaller ones (*Galenus's pulse*).

As long as the conditions of the myocardium are good, the *stroke volume* is directly proportional to the length of the preceding diastole and inversely proportional to the stroke volume of the preceding cycle. (This, however, is approximate and not exact.) If there is cardiac failure, no rule can be established The *speed* of the small pulse waves is always greater than that of the large waves

Electrokymogram. This tracing has been studied by Lewis and Terry, Boone et al., and Engstroem et al The atrial tracing shows the absence of atrial waves The waves of the ventricular and arterial tracings (both the aortic and the pulmonic) have a variable amplitude, which is roughly proportional to the length of the previous diastole

PREMATURE BEATS

Jugular Tracing *Atrial premature beats* have A, C, and V waves which are similar to those of a normal tracing *Nodal* and *ventricular premature beats*, on the other hand, frequently have a high A wave, because of simultaneous atrial and ventricular contraction which is accompanied by a venous regurgitant wave

A *left ventricular premature beat* may show a delay of V over the 2d aortic sound (early contraction of the left ventricle, later contraction of the right, with late opening of the tricuspid valve).

Arterial Tracing, Hemodynamics. The pulse wave of the premature beat may be as high as a normal wave and occasionally higher *It is usually smaller and may be absent* on account of small ejection or even lack of ejection. Records taken over different arteries *show that* the pulse wave of the *premature* beat may be present in the arteries near the heart (carotid) and absent in those distant (tibial arteries) A drop in pressure occurs during the compensatory pause The following wave is higher than normal, and is followed by a smaller wave; this may start a *pulsus alternans*

The pulse of the premature contraction has a low systolic and a high diastolic pressure, while the following pulse is much larger, having a high systolic and a low diastolic pressure.

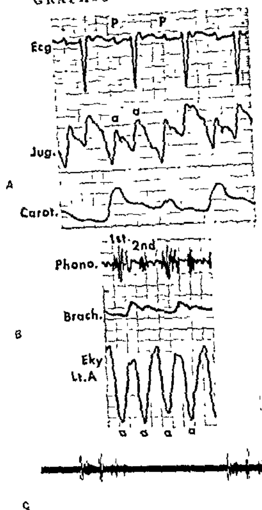


Fig. 11-18. Tracings revealing a greater number of atrial waves than ventricular waves. A. Multiple waves of atrial origin in the jugular tracing of a patient with atrial flutter B Multiple waves in the left atrial border electrokymogram of a patient with atrial flutter. C Multiple waves in the right atrial border electrokymogram in a patient with complete AV block Above, phonocardiogram; below, EKy.

From *two to three* pulse waves are necessary *for reaching* again a normal and stable level of blood *pressure*. On the other hand, the first normal contraction following *an interpolated premature beat* frequently yields a smaller *pulse* wave in the peripheral arteries (a short *diastole* precedes such an extrasystole).

The pulse wave of a *right* ventricular premature beat *may* be delayed over the beginning of the corresponding *1st* apical sound

7

Graphic tracings in arrhythmias and atrioventricular block

ALDO A. LUISADA

SUPRAVENTRICULAR TACHYCARDIA

Jugular Tracing. There is only one high wave, owing to fusion of the various waves If the atrial and ventricular contractions occur exactly at the same time, this venous wave becomes high, because if the right atrium cannot push the blood forward against the closed tricuspid valve, it will push it backwards, into the large veins

Arterial Pulse. The pulse becomes small during the attack. The dicrotic wave, however, may be relatively higher, and its fusion with the following pulse wave may simulate an anacrotic pulse The speed of the pulse wave is often reduced

VENTRICULAR TACHYCARDIA

Jugular Tracing. High atrial waves are recorded, at a rate which is slower than that of the arterial pulse (unless there is atrial fibrillation). The waves may be slightly irregular

Arterial Tracings. The pulse waves are small and may show a variable height, then, a higher wave is caused by the casual precedence of an atrial contraction over a ventricular. There may be *pulsus alternans.*

ATRIAL FLUTTER

Low-frequency Tracing of the Precordium. Atrial waves may be recorded in the intervals between the ventricular waves of this tracing.

Jugular Tracing. Regular atrial waves were recorded by several workers. More recently, Contro has recorded high atrial waves in five cases of flutter by means of a linear microphone and an amplifier. These waves give evidence of the coordinated contractions of the atria.

Electrokymogram. If the slit of the pickup is placed across the border of either atrium, good evidence of atrial contractions can be secured (Fig. 11-18A, B). The atrial waves are usually of large amplitude, and their detection is important in cases where the electrocardiographic tracing had led to admission of "impure fibrillation."

ATRIAL FIBRILLATION

Jugular Tracing. The C and V waves follow each other with complete irregularity. There are no A waves, because of the fibrillation

Low-frequency Tracing of the Precordium. The waves caused by ventricular contraction are of various height and configuration. When diastole is short, the subsequent isometric tension period becomes longer. The height of the waves varies somewhat but is not exactly proportional to the length of the preceding diastole.

Arterial Tracings, Hemodynamics. The pulse waves are typically irregular, having various heights, lengths, and configurations Patients in congestive failure often have a *pulse deficit* because some of the ventricular contractions have such a small ejection that they are not followed by a pulse wave. However, when ejection is small, waves may be present in the

8

Phonocardiography in arrhythmias and blocks

ALDO CALO

SUPRAVENTRICULAR TACHYCARDIA

The findings during the attack should be considered separately from those obtained after reestablishment of sinus rhythm. The latter may be considered as the result of a posttachycardial phonocardiographic syndrome

The Attack. Increased loudness of the 1st sound is frequent. Even though loudness may progressively increase during the first few beats of the attack, once the maximum loudness has been reached, the 1st sounds continue with the same magnitude, small variations in amplitude may be due to respiratory variations The increased loudness of the 1st sound may be caused either by summation of the 1st with the 4th (atrial) sound, or by changes in the mechanism of closure of the AV valves

In *low nodal tachycardia with retrograde conduction*, the atrial sound may show up in the tracing soon after the 1st sound, causing *splitting of the 1st sound* (Fig. 11-19A) Actually, it is not a *real splitting* but the addition of a *new sound* (atrial) in early systole *Alternans* is exceptional If present in the above cases, alternans affects *only* the ventricular *component*, *i e*, the 1st sound, while the *atrial* sound is unaffected. The *2d sound may be* accentuated, split (either occasionally or continuously), or small, to the *point* of disappearance Both *systole and diastole* are markedly *shortened*, the latter more than the former As diastole becomes progressively *shorter* and the atrial contraction is closer to the rapid filling of the preceding cycle, a *summation type of triple rhythm* (*summation* gallop) occurs. Several *murmurs* may appear during attacks of tachycardia of long duration. They have been explained as the result *of increased speed of* flow, changes *of the* normal sequence of atrial and ventricular contractions, or relative insufficiency of the mitral valve The latter *might* be due to ventricular dilatation as a result of strain On the contrary, preexisting murmurs caused by valvular lesions *or shunts may disappear during an* attack.

Posttachycardial Syndrome. The phonocardiographic signs of this syndrome *may consist of changes of the sound* and murmurs present before the attack; disappearance of signs brought about by the attack itself; return of signs obscured by *the attack*, and, finally, appearance of new phonocardiographic data. After sinus rhythm is reestablished, the following may be found: 1st *and* 2d sounds—true or false splitting, alternans may either decrease or disappear. Systole and diastole regain their normal values A summation *type* of triple rhythm, originated by the attack, may disappear. *On the* other hand, a new triple rhythm may appear after the attack because of myocardial insufficiency. The same may be said for *murmurs which* may disappear, *reappear, or start* after the attack. These murmurs are usually of mitral origin and *are functional.*

ATRIAL FLUTTER

In most cases, the *atrial sounds*, which on *occasion may* become abnormally large and even clinically audible, may have no time re-

(earlier contraction of the right ventricle, subsequent contraction of the left, responsible for the pulse).

The *stroke volume* varies greatly, being inversely proportional to the length of the preceding diastole. Therefore, the earlier the contraction, the smaller the stroke volume. The compensatory pause is followed by a contraction which has a proportionally larger stroke volume. This, however, is not true if the myocardium is weak.

The speed of the pulse wave is directly proportional to the level of diastolic pressure; therefore, the weak pulse of the premature contraction has a greater velocity than the others.

Blood Pressure Tracings. Different levels of blood pressure can be obtained if the premature beats occur periodically. (1) those corresponding to the systolic and diastolic pressure of the normal pulse waves, (2) those corresponding to the pulse waves of the premature beats (low systolic, high diastolic); and (3) those corresponding to the pulse waves immediately subsequent to the premature beats (high systolic, low diastolic).

Low-frequency Tracing of the Precordium. The premature contraction may give waves of normal configuration The isometric tension period is often prolonged. This may cause bizarre or large waves.

Electrokymogram. Premature contractions are easily studied by means of border tracings of the left ventricle, the pulmonary artery, or the aortic arch If simultaneous tracings of the left ventricle and one of the arteries (aorta or pulmonary artery) are taken, conclusions may be drawn about the site of origin of a ventricular premature beat. The aspect of the tracing depends upon the time of the cardiac cycle at which the premature contraction occurs and the phase of the ventricular filling

If the contraction starts early in diastole, its amplitude is small, isometric contraction is prolonged, and the curve assumes a more peaked aspect. The isometric tension period may last more than 0.06 sec on account of both the high level of arterial pressure and the small amount of ventricular blood If the contraction takes place immediately after the T wave, no ejection may occur During the compensatory pause, an abnormally large filling of the ventricles takes place. This, plus the lower level of arterial pressure, causes a shortening of the isometric tension period of the following contraction.

ATRIOVENTRICULAR BLOCK

Jugular Tracing. The A waves are normal in shape and follow each other, usually, at a normal rate; the C and V waves occur at regular, but much longer, intervals. Therefore, more than one A wave is found between a V wave and the next C wave. Occasional coincidence of an A wave with a C or V wave may occur, with a resulting higher wave.

Arterial Tracing. A high and slow pulse is recorded. An anacrotic depression is frequently present in the ascending branch of the pulse curve. Multiple undulations follow the dicrotic wave.

In *occasional block*, the tracings reveal the occasional absence of a pulse wave (*intermittence*). In *periodic block*, the series of pulse waves shows a periodic increase in the pause separating two pulses, then a longer pause with a deeper pressure drop. *Interference dissociation* may cause a bigeminal rhythm, the second wave being paradoxically *higher* than the first (Fischer).

Low-frequency Tracing of the Precordium. High atrial waves are present between the waves caused by the ventricular contractions

Electrokymography. The electrokymogram of AV block has been studied by the author, Engstroem et al., and Pannier et al

ATRIAL TRACINGS If atrial contraction falls during ventricular systole, the atria decrease in volume as in normal subjects; apparently the blood is pushed backwards into the veins. If the atrial contraction falls during ventricular diastole, the pattern consists of an oblique, descending line during atrial contraction, and a less steep rise subsequent to it. The depth of the contraction varies, it is usually larger when the atrial contraction falls during a ventricular contraction because of additional ventricular pull (Fig. 11-18C).

LEFT VENTRICULAR TRACING. The tracing of the left ventricle may not show any effect of the atrial contractions. If it does, the latter are revealed by small positive waves.

lationship with the main heart sounds. In other cases, changes of cardiac sounds, murmurs, and intervals may be produced by a profound alteration in the hemodynamics caused by the disturbance of rhythm (Fig. 11-19B). The atrial sounds recorded from the esophagus start 0 04 sec after the P waves, most likely they are produced within the atria The atrial sounds recorded over the precordium are far more delayed because they start from 0 14 to 0 24 sec after the P waves and 0 10 sec after the A waves of the jugular tracing Thus indicates that the precordial atrial sounds are originating either in the ventricular walls or in the AV valves. In general, each atrial sound consists of a single group of 1 to 4 low-pitched vibrations, lasting from 0 03 to 0 08 sec. Exceptionally they last 0 16 sec and present two separate components, one with a single high vibration, and the other with several lower vibrations (see Atrioventricular Block, further on in this chapter, for explanation) The amplitude of atrial vibrations is usually small, but in certain cases they may be one-half of either heart sound Sounds produced during systole are often higher than those originated in diastole In irregular flutter, the amplitude of these sounds is variable and some of them may be absent in spite of ECG evidence of atrial contractions The modifications of cardiac sounds, murmurs, and intervals produced by *regular flutter* are constant, while variable and inconstant findings are found in *irregular flutter*, where marked changes of dynamics occur

The changes of the 1st sound are closely related to the duration of the P-R interval or P-1st sound interval, which are equivalent For values between 0 08 and 0 12 sec, the 1st sound is increased in loudness (an occasional increase is typical of irregular flutter) For higher or lower values, the 1st sound either may be decreased or may present a systolic or presystolic addition of an atrial sound (*pseudo splitting*) The *1st sound* may be delayed over the beginning of the QRS complex, may be of small amplitude, and may be alternating The *2d sound* may be increased, decreased, or split In irregular flutter an occasional accentuation may be due to addition of an *atrial sound* to the 2d sound At times, the 2d sound may disappear because of weak ventricular systole, as in some types of extrasystoles or cases of atrial fibrillation. A *summation type* of triple rhythm can take place whenever an atrial contraction coincides with the phase of rapid ventricular filling. In regular flutter, this may happen after every ventricular systole; in irregular flutter, it may happen occasionally.

It is a common notion that the *presystolic murmur* of mitral stenosis disappears whenever the left atrial contraction fails to occur. The fluttering left atrium may display such a powerful systole as to accelerate the flow across the mitral valve. This results in *a loud murmur for every atrial contraction* which takes place in diastole (in systole, it is obvious that the atrium cannot open the mitral valve). The *systolic murmur* of mitral insufficiency may disappear or change in character during atrial flutter, and it may reappear or increase after reestablishment of the sinus rhythm.

ATRIAL FIBRILLATION

Atrial fibrillation is characterized by a complete arrhythmia of cardiac sounds and murmurs with irregular variations for every cycle. An exception is represented by rare cases with idioventricular rhythm

Cases without Valvular Lesions. The 1st sound is usually *delayed* over the R wave but this delay is *small*. Its amplitude and duration are variable, so that the 1st sound may become quite small or very large Apparent splitting is frequent; this may be due to a separation of the valvular components or, in the case of a very short diastole, to the occurrence of a ventricular type of triple rhythm (gallop) immediately followed by the 1st sound (Fig 11-19C) *The 2d sound usually presents* continuous changes of amplitude and duration which are independent from those of the 1st sound There also may be an occasional splitting due to asynchronism of the semilunar valves

In some cases, the apical phonocardiogram may show *a short systolic murmur*, which, in the absence of any valvular lesion, is thought to be due to functional mitral insufficiency or to the formation of eddies Even though no atrial or summation type of triple rhythm may occur on account of the lack of atrial contractions, various types of triple rhythm may occur. These are due to the addition of a ventricular sound which may fall in early diastole, mid-diastole, or just prior to the following 1st

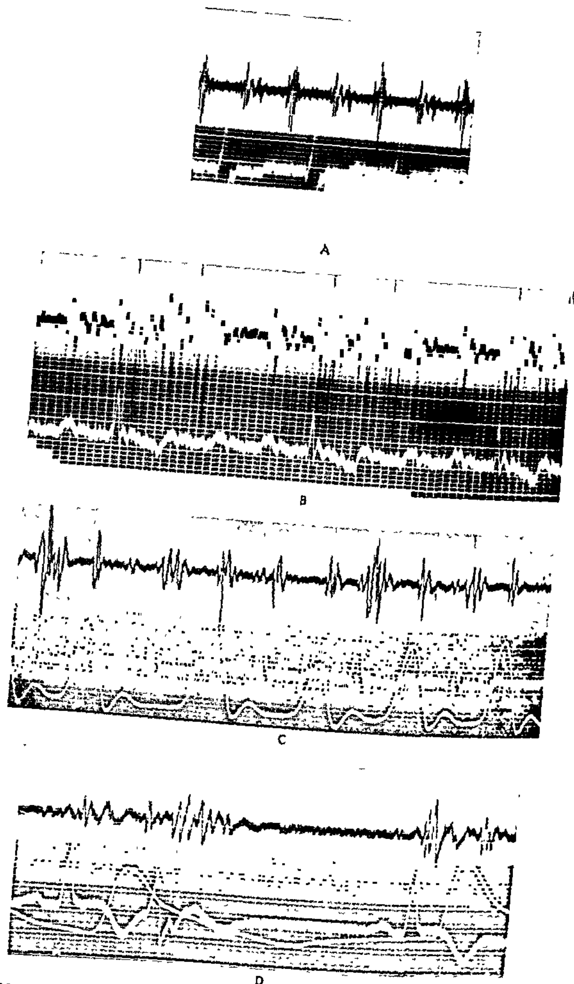


Fig. 11-19. A. Supraventricular tachycardia. Phonocardiogram (stethoscopic) 2R2. B. Atrial flutter. Phonocardiogram (stethoscopic) 2R2. C. Atrial fibrillation. Phonocardiogram (stethoscopic) 5L7-O S. D. Ventricular extrasystole. Phonocardiogram (stethoscopic) 4R2 Od.

and murmurs may disappear if present, or, on the contrary, may appear during the attack.

2 *Posttachycardial syndrome.* Decreased loudness of the cardiac sounds, murmurs due to relative valvular insufficiency, and triple rhythm are frequent. Following ventricular tachycardia, one can see a marked decrease in amplitude of the 1st sound, a systolic murmur in decrescendo, and a triple rhythm (summation type). The last two had disappeared during the attack but were previously present.

NODAL RHYTHM

The changed time relationships between atrial and ventricular systoles cause marked changes of the phonocardiogram. If present, an atrial *4th sound* disappears. The vibrations of the 1st sound, owing to closure of the AV valves, have an amplitude which varies in proportion to the P-R interval. This is because of different tension of these valves at the beginning of systole. In nodal rhythm, the 1st sounds have constant loudness, while in cases of wandering pacemaker, there are continuous changes. A short systolic sound due to atrial contraction may appear.

SINOATRIAL BLOCK

There are only two published phonocardiograms in cases with bigeminal SA block. The cardiac sounds either remain unchanged, or they alternate in amplitude, number of vibrations, and duration (Fig. 11-21A).

ATRIOVENTRICULAR BLOCK

Complete Atrioventricular Block without Valvular Lesions. *Atrial sounds* are present both in systole and diastole (Fig. 11-21B). In esophageal phonocardiograms and, occasionally, in precordial tracings, they present *three groups of low-pitched vibrations:* the first is caused by the atrial contraction, the second seems to be due to the resulting ventricular distention or a vibration of the AV valves, the third, to an elastic recoil of the ventricular walls. In precordial tracings, where the three groups are recorded, they occur 0.04, 0.12, and 0.27 sec after the respective P wave, and the duration of the atrial sound complex is from 0.34 to 0.36 sec. However, the first group of vibrations is seldom recorded. Then the atrial sound complex starts 0.06 to 0.12 sec after the P wave and lasts from 0.15 to 0.22 sec. The atrial sounds during systole consist of one or two groups of vibrations, and they can be larger than the diastolic. Their mechanism of production is still discussed. Some authors feel that these sounds are directly caused by atrial contraction which causes a vibration of the closed AV valves. *Atrial murmurs* can be seen in diastole in older patients 0.14 to 0.23 sec after the beginning of the P wave. These murmurs, occurring *after* atrial contraction, can be explained by sclerosis of the AV valves, which at first hinders their upward movement, causing a moderate regurgitation, and then delays their opening, thus slowing the normal

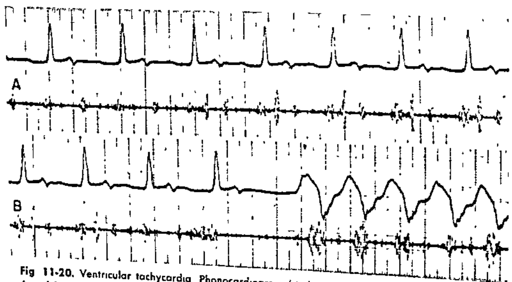


Fig 11-20. Ventricular tachycardia. Phonocardiogram (stethoscopic) 3M. (0.02 in. and 0.10 in.). A and B are consecutive sections of the same tracing.

sound, on account of the variable duration of diastole.

Cases with Mitral Lesions. Frequently the sclerosis of the mitral cusps increases the loudness of the 1st sound and causes its splitting. The Q-1st sound interval, which is particularly prolonged in mitral stenosis, becomes even longer if there is atrial fibrillation. This interval is inversely proportional to the duration of the preceding cardiac cycle: shorter diastole = longer interval (Luisada, Cossio). The *opening snap* of the mitral valve has duration and intensity which vary for every cycle (Rappaport and Sprague; Wells). This snap is more distant from the 2d sound when left atrial pressure is lower; therefore, it is more distant after a long diastole. *Murmurs* of mitral origin are known to disappear when atrial fibrillation starts. This is particularly true for the presystolic murmur, while the systolic and the mid-diastolic murmurs may disappear for a time and reappear later. On the other hand, the mid-diastolic murmurs of mitral stenosis may be louder than in cases with sinus rhythm. This may be explained by the fact that left atrial pressure is higher. A *ventricular type* of triple rhythm is frequent in mitral insufficiency, occasionally present in moderate mitral stenosis, and absent in severe mitral stenosis. It may simulate an opening snap

EXTRASYSTOLES

Extrasystoles (Fig. 11-19D) are characterized by the premature appearance, and possibly by the occasional absence, of cardiac sounds and murmurs Other possible signs are due to the extrasystole itself. Others may affect the preceding cycle (preextrasystolic signs) and some of the following beats

The 1st sound is usually accentuated and delayed, the Q-1st sound interval being from 0 08 to 0 10 sec and even 0.12 sec The main vibrations may be from two to four times higher than those of the normal contractions Sometimes the 1st sound is decreased and may be completely absent, it may be either shortened or prolonged, it may be split, but this is seen only in ventricular extrasystoles, on account of marked asynchronism of closure of the mitral and tricuspid valves.

Ventricular systole is usually short The *2d sound is usually small* and may become so faint as to disappear. This is more frequent in cases of early extrasystoles, especially if they are interpolated. Absence of both sounds is extremely rare; in such cases, *the extrasystole is clinically mute.* Because of asynchronism of the closure of the semilunar valves, splitting of the 2d sound may occur in ventricular extrasystoles. On the other hand, previous splitting of the 2d sound may disappear during the extrasystole.

Triple Rhythms. The atrial type disappears in ventricular extrasystoles because of the absence of atrial contractions. On the other hand, following an extrasystole, a ventricular type of triple rhythm may occur, or it may disappear if it was regularly present in the normal cycles. A summation type of triple rhythm may be seen in atrial or sinus premature contractions It is due to coincidence of the rapid filling of the preceding beat with the following atrial contraction. Extrasystoles may either increase or decrease the loudness of *murmurs* The latter may even disappear during an extrasystole because of inadequate filling of the ventricles

The extrasystoles may modify some of the graphic characteristics of the preceding cardiac cycle For instance, when they occur very early, the 1st sound may coincide with a 3d sound, and even with the 2d sound of the previous cycle This may cause increased loudness of that 2d sound, a summation type of triple rhythm, or an accentuation of the early-diastolic murmur of mitral stenosis. On the other hand, this murmur may disappear if several premature contractions occur in a row.

The 1st sound is frequently increased in the beat immediately following the extrasystole and, at times, in the second or third subsequent beat. Occasionally, *alternans* develops.

VENTRICULAR TACHYCARDIA

The phonocardiographic signs of the ventricular tachycardias are similar to those of the supraventricular forms.

1. *The attack.* During the attack, ventricles and atria beat independently and, now and then, contract at the same time. The 1st sound presents characteristic changes consisting of occasional sudden increase of loudness (Fig 11-20). The 1st sound may be prolonged or split, either constantly or intermittently, and is usually delayed. The 2d sound occurs early (short systole). Diastole is even shorter. As in supraventricular tachycardia, triple rhythms

and murmurs may disappear if present, or, on the contrary, may appear during the attack.

2 *Posttachycardial syndrome.* Decreased loudness of the cardiac sounds, murmurs due to relative valvular insufficiency, and triple rhythm are frequent Following ventricular tachycardia, one can see a marked decrease in amplitude of the 1st sound, a systolic murmur in decrescendo, and a triple rhythm (summation type). The last two had disappeared during the attack but were previously present

NODAL RHYTHM

The changed time relationships between atrial and ventricular systoles cause marked changes of the phonocardiogram If present, an atrial *4th sound* disappears. The vibrations of the 1st sound, owing to closure of the AV valves, have an amplitude which varies in proportion to the P-R interval This is because of different tension of these valves at the beginning of systole In nodal rhythm, the 1st sounds have constant loudness, while in cases of wandering pacemaker, there are continuous changes A short systolic sound due to atrial contraction may appear

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Complete Atrioventricular Block without Valvular Lesions. *Atrial sounds* are present both *in systole and diastole* (Fig. 11-21B). In esophageal phonocardiograms and, occasionally, in precordial tracings, they present *three groups of low-pitched vibrations:* the first is caused by the atrial contraction, the second seems to be due to the resulting ventricular distention or a vibration of the AV valves, the third, to an elastic recoil of the ventricular walls In precordial tracings, where the three groups are recorded, they occur 0 04, 0.12, and 0 27 sec after the respective P wave, and the duration of the atrial sound complex is from 0 34 to 0 36 sec. However, the first group of vibrations is seldom recorded Then the atrial sound complex starts 0 06 to 0.12 sec after the P wave and lasts from 0.15 to 0 22 sec The atrial sounds during systole consist of one or two groups of vibrations, and they can be larger than the diastolic. Their mechanism of production is still discussed Some authors feel that these sounds are directly caused by atrial contraction which causes a vibration of the closed AV valves *Atrial murmurs* can be seen in diastole in older patients 0.14 to 0.23 sec after the beginning of the P wave. These murmurs, occurring *after* atrial contraction, can be explained by sclerosis of the AV valves, which at first hinders their upward movement, causing a moderate regurgitation, and then delays their opening, thus slowing the normal

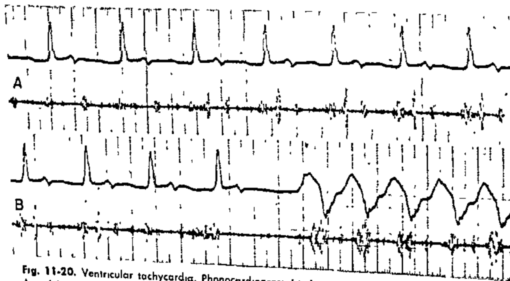
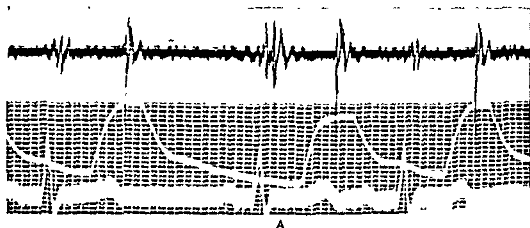


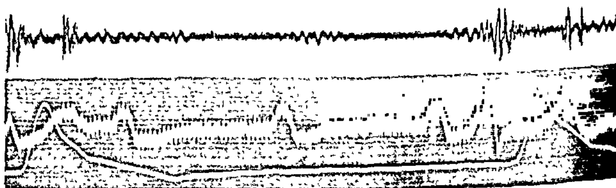
Fig. 11-20. Ventricular tachycardia. Phonocardiogram (stethoscopic) 3M. (0 02 in and 0 10 in). A and B are consecutive sections of the same tracing.

ventricular filling. In other words, slight insufficiency and stenosis would take place in turn, both of them functional and of short duration.

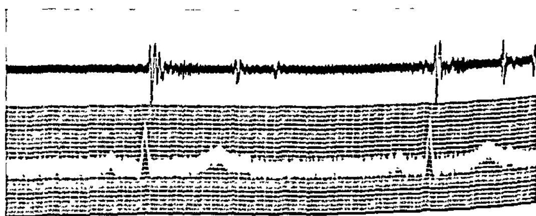
FIRST SOUND. *Splitting* of the 1st sound has been described. It is due to two separate groups of ventricular vibrations. Splitting may be simulated by presystolic or systolic occurrence of an atrial sound. *Changes in amplitude of the 1st sound* are also typical of complete AV block. In long tracings, one can see marked changes in amplitude from one beat to the next. The 1st sound may disappear almost completely, or it may increase in amplitude up to five or six times (*cannon sound*). The frequency, duration, and number of vibrations of the 1st sound usually follow the changes in amplitude. Thus, an increased 1st sound has a higher pitch and more vibrations. A definite relationship has been found between the amplitude of the 1st sound and the duration of



A



B



C

Fig. 11-21. A. Sinus bigeminy. B Complete AV block C. Incomplete AV block with Wenckebach periods. All phonocardiograms (stethoscopic) 5L6

the P-R *interval* For P-R intervals from 0 50 to 0 32 *sec*, the amplitude of the 1st sound is somewhat *increased*, from 0 32 to 0.23 sec, the amplitude is *decreased*; from 0 25 to *0.12* sec, it is moderately increased, from 0 14 to 0 04 sec, it is again *markedly increased* (cannon sound). When the P wave follows *the R wave* and *there is an* R-P *interval of from* 0 04 *to* 0 28 *sec*, the sound *is just slightly increased*

A *dissociated cannon sound* and a *double cannon sound* were described in cases of complete AV block with bundle branch block. The former is due to accentuation *of one of* the two components of a split 1st sound, the latter to accentuation of both components *The* variable amplitude of the 1st *sound has* been explained by the different position of the AV valves at the beginning of the systole and by different tension of their fibrous rings.

A systolic murmur, probably due to relative mitral insufficiency, is frequent. The formation of eddies in an overloaded and distended ventricle could also be considered as a possible cause.

The 2d sound shows changes *in time* and amplitude, and it may *be split*. The sound *is* delayed *in* regard *to the* 1st sound *because of* prolongation *of mechanical systole*, *but may* precede the end of the T wave on *account of* even more prolonged electrical systole. An occasional increase of the 2d sound occurs when the P wave coincides with the end of the T wave. *False splitting* occurs if an atrial sound falls just before the 2d sound, *true splitting* when two valvular components are separate. The former shows the low-grade *vibrations* of the atrial sound, the second has two groups of similar vibrations.

Triple rhythms have the usual graphic characteristics. The additional sound occurs periodically. It may occur intermittently every time that a P wave follows the T wave, i.e., any time that the atrial contraction coincides with rapid ventricular filling.

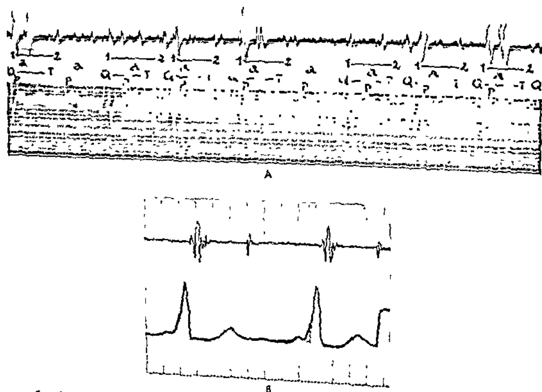


Fig 11-22. A. Incomplete AV block with Wenckebach periods. Phonocardiogram (stethoscopic) 516. B Wolff-Parkinson-White syndrome Phonocardiogram 0–25 cps 517.

Atrioventricular Block with Mitral Lesions. The valvular lesion frequently causes the 1st sound to be less decreased than when the mitral valve is normal. The systolic murmur of mitral insufficiency may decrease or disappear if there is a short P-R interval; this is because atrial contraction somewhat resists the regurgitant jet (only for a short time) and gives a greater tension to the mitral ring. Every atrial contraction may be followed by a *murmur,* during the long diastole, three or four murmurs may be seen with regular intervals and progressively decreasing amplitude. This is because the increased diastolic filling of the ventricles gradually hinders further filling due to atrial propulsion.

Incomplete Atrioventricular Blocks. In a 2:1 block, one may see *two atrial sounds,* one in protodiastole and one in presystole (Fig. 11-21C) The former may coincide with and accentuate the 2d sound, it may fall during rapid filling, thus causing a summation type of triple rhythm, or it may give a delayed diastolic sound. In cases without valvular lesions, every P wave may be followed by an atrial murmur, as in complete AV block, in cases with mitral stenosis, the P wave may be followed by a loud diastolic murmur. In both cases, a short systolic murmur is also usually present. In *Wenckebach periods,* the diastolic atrial sounds parallel the cyclic variations of the P-R interval. This holds true both for the presystolic murmur of mitral stenosis and for the atrial sounds and murmurs in cases without valvular lesions (Fig 11-22A). The magnitude of the 1st sound varies according to the duration of the P-R interval; it may become progressively decreased, accentuated, or split.

FIRST DEGREE OF ATRIOVENTRICULAR BLOCK Phonocardiographic evidence of atrial activity (sounds, murmurs) occurs earlier in regard to the 1st sound. If tachycardia is present, such murmurs may even become mid- or early diastolic. Thus, they may coincide with the opening snap of the mitral valve, with a 3d sound, or with the early diastolic murmur of mitral stenosis Unusual auscultatory rhythms may arise in this way.

Wolff-Parkinson-White Syndrome. Only a few phonocardiograms have been published to date. The interval Q-1st sound is normal; the 1st sound has a normal magnitude (Fig 11-22B). The 2d sound is neither split nor delayed. A 3d sound may be recorded. These data may be interpreted as indicating that (1) there is no bundle branch block (in the normal sense), (2) the P-R interval is only apparently shortened, (3) AV valves closure occurs at a normal distance from the P wave, in spite of the so-called *delta wave.*

9

Bundle branch and intraventricular block

Bundle Branch Block; Intraventricular Block

AARON B. BENCHIMOL AND PAUL SCHLESINGER

Graphic Data in Bundle Branch Block

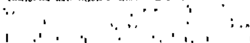
ALDO A. LUISADA

BUNDLE BRANCH BLOCK

MODERN CONCEPTS OF VENTRICULAR ACTIVATION

The bundle branch block concept rests upon the knowledge of the process of ventricular activation *which takes place in the conducting* tissues of the heart, originating in the SA node, spreading *through the atria to the AV node,* the bundle of His and its two stems, and finally *reaching the myocardial* fibers through the subendocardial Purkinje network

When one of the branches of the bundle of His fails to conduct the stimulus, the order of ventricular activation is modified and certain elec-



the right or the left bundle branch is involved but also upon the severity of the lesion and the degree of conduction disturbance

According to studies of Sodi Pallares et al (1956), the first part of the ventricular myocar*dium to be activated is the interventricular septum,* which is no longer considered as a syncytial mass, but rather as *two separate portions, separated by a "barrier," in which the muscle fibers are diversely oriented with multiple synaptic connections,* in addition, these septal fibers have different polarities

The greater part of the septum belongs to the left ventricular myocardium, so that it forms the entire posterobasal aspect of the septum, which is completely devoid of right ventricular fibers. Thus, *the left ventricle encroaches upon certain areas of the endocardial surface of the right ventricle,* and an electrode placed at this point may actually *record left ventricular* potentials. The right ventricular component of the septum represents only *a minor fraction of its entire mass.*

The interventricular septum is activated from both the right and left endocardial surfaces *The left bundle branch is responsible for the activation of the entire left septal surface, as well as for most of the septum proper, whereas the right branch supplies a very small portion of this structure*

Since the left ventricular septal mass is greater than that pertaining to the right ventricle, it is obvious that the resultant vector *is directed from* left to right

The beginning of ventricular activation takes *place at the middle third of the septal surface,* and spreads from left to right, anteriorly and upwards The last points to be activated are the *anterobasal portions of the right septal surface*

The right surface of the septum is normally activated *0 01 sec after the left, whereas the last* portions are activated 0 03 sec later (Fig. 11-23A).

The initial septal vector is responsible for the small Q wave which is usually recorded in the leads overlying the left ventricle, and which is due to activation of the left *septal* mass This process

is initiated at the left ventricular endocardium and spreads toward the septal fibers at the base of the anterior papillary muscle of the right side of the septum, which at this level is probably still formed by the left ventricle.

The late activation of the basal portions of the septum is due to the scarcity of the Purkinje network at this level. It probably contributes to a great extent to the third cardiac vector (so-called "final vector"), although this is variable from one individual to the other.

Following the initial septal activation, the depolarization process spreads to the free walls of both ventricles perpendicularly, from the endocardium to the epicardium. Studies of Prinzmetal et al (1953) confirmed by Sodi Pallares (1956) have demonstrated that approximately two-thirds of the subendocardial aspects of the free walls of both ventricles are simultaneously and almost instantaneously activated, having practically no electrocardiographic representation. The potentials obtained in this area are similar to those recorded in the ventricular cavities, this portion of the myocardium was designated as the *electrical endocardium*, since from the standpoint of cardiac activation, it merely represents an extension of the cavity. The spread of excitation through the electrical endocardium is extremely rapid, having an approximate speed of 2,000 to 4,000 mm/sec. This is explained by the deep penetration of the Purkinje fibers into this part of the cardiac muscle.

The activation of the free wall of the ventricles is responsible for the second cardiac vector, which is primarily due to the predominance of electrical forces of the left ventricle, ten times greater than those of the right ventricle, the latter being insignificant from the standpoint of the vectorial analysis of the electrocardiogram in normal individuals (Fig. 11-23B).

This second cardiac vector is generally of great magnitude, is directed toward the left, posteriorly and downwards, and is seldom influenced by the right ventricle (this may occur in cases of extreme right ventricular hypertrophy). The predominance of the electrical forces of the left ventricle in cardiac activation explains the counterclockwise rotation of the normal vectorcardiogram in the horizontal plane.

The process of activation varies according to the degree of block. Thus, it becomes important to distinguish between complete and *incomplete bundle branch blocks.* This concept was established on the basis of experimental studies (Rodriguez and Sodi Pallares), by comparing the electrocardiograms obtained in dogs with various degrees of bundle branch block, and those of a human being's tracing with

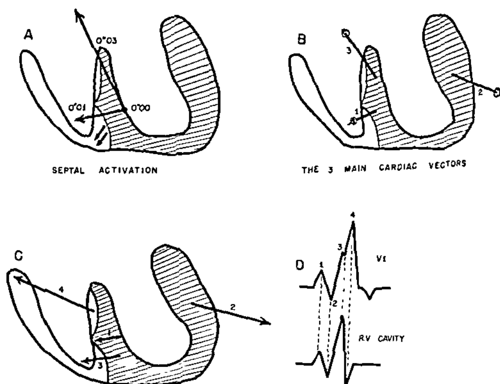


Fig. 11-23. A Septal activation. B The three main cardiac vectors C and D. Schematic representation of the four vectors resulting from ventricular activation in right bundle branch block, and the corresponding deflections in lead V_1 and in the right ventricular cavity.

similar configurations. It was observed that the *complete section* of one of the branches of the bundle of His was followed by a remarkable increase in the *duration* of the QRS interval and by a considerable delay in the intrinsicoid deflection, with secondary T-wave changes over the homolateral ventricle, in addition to a prolongation of electrical systole. These changes were characteristic of the complete type of bundle branch block. If instead of making a complete section, the upper part of *the interventricular septum* (*where the bundle branch crosses this area*) was compressed, it was observed that for short periods of time, QRS complexes were recorded similar to those of the previous experiment, the latter became progressively normal, with an intermediate stage during which a configuration similar to that of complete bundle branch block was obtained, although of shorter duration, these were designated as *incomplete bundle branch blocks.*

Notwithstanding the number of objections to the concept of bundle branch block in man, especially that of its septal mechanism, the above configurations represent, in the majority of cases, various degrees of conduction disturbance in one of the branches of the bundle of His causing ventricular asynchronism. This concept has been confirmed experimentally, pathologically, by intracavitary tracings and precordial leads, and by mechanical recordings showing ventricular asynchronism. Studies of Sodi Pallares on the mechanism of septal activation and experimental bundle branch block have contributed a great deal to a better understanding of this problem, confirming and extending knowledge of these conduction disturbances.

VENTRICULAR ACTIVATION IN BUNDLE BRANCH BLOCK

Right Bundle Branch Block. In all degrees of right bundle branch block, including the complete type, the wave of excitation crosses the *left septal* mass, which forms the majority of the septum, following the normal pathway with no change either in direction or velocity (1,000 to 1,200 mm/sec). However, there is a *late arrival* of the wave of *excitation* to the right side of the septum, with a considerable delay (0.06 *sec instead* of 0.01 to 0.02 sec) after the activation of the left side. This conduction delay is due not to uniform slowing of the wave of excitation *in* the entire septal mass, but rather to slower progression in a small area of the myocardium which is very close to the right surface, forming a "barrier" which separates the regions normally supplied by the left bundle branch from the area activated by the right branch. This has been proved experimentally by Sodi Pallares et al (1956) using bipolar leads, with the electrodes placed very close to one another, and including the intramural potentials.

From a vectorial point of view, four main vectors can be schematically identified in right bundle branch block representing the sequence of ventricular activation in these cases (Fig. 11-23C, D).

Vector 1 corresponds to the *normal septal vector,* since this phase of the activation process is unaltered in right bundle branch block, and determines the small Q waves in leads overlying the left ventricle, as well as the small initial positive deflection obtained both in the cavity of the right ventricle and over its epicardial surface.

Vector 2 represents the *activation of the free wall of the left ventricle* and is responsible for a small S wave recorded in the *right ventricular* cavity and over the right ventricular *epicardium,* since it is directed from right to left.

Vector 3 corresponds to the *powerful septal forces which are directed from left to right in the lower part of the septum,* and which develop when the wave of excitation crosses the barrier between left and right septal masses with a considerable delay. This vector is of great magnitude, as it is due to a slow type of activation, and it is well known that the slower the velocity of the excitation wave, the more powerful are the corresponding vectorial forces. In view of its great magnitude, it partially neutralizes the previous one corresponding to the activation of the free wall of the left ventricle, and explains the small amplitude of these forces. The third vector is responsible for the right intracavitary R′ and for most of the initial segment of the right epicardial R′.

Finally, *vector 4* probably *represents a summation of the activation of the upper portions of the septum and the free wall of the right ventricle,* determining the peak of R′ over the right ventricular epicardium and that of S′ recorded in the cavity of the right ventricle.

Left Bundle Branch Block. In right bundle branch block, *it is difficult to d*[illegible] e [illegible] e [illegible] *from left to right,* as in normal individuals. Thus, it is *impossible* to detect the exact instant when the *activation* crosses the

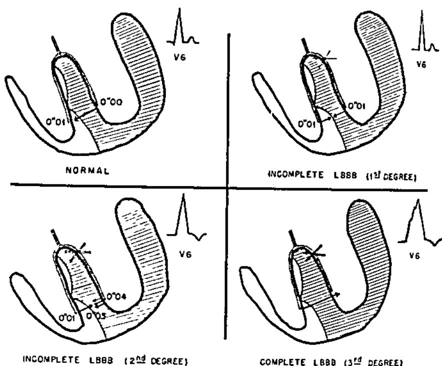


Fig. 11-24. Septal activation in the normal heart and in the three degrees of left bundle branch block with the corresponding ventricular complexes in the left precordial leads.

septal barrier However, this does not apply to left bundle branch blocks, in which different types of activation are observed in relation to the degree of this conduction defect. According to Rodriguez and Sodi Pallares, three types of left bundle branch block must be distinguished (Fig. 11-24):

1. *First degree* There is only a slight delay in the spread of the stimulus in the left branch of the bundle, resulting in a *late activation of the left septal surface*, without any change in the direction or speed of the excitation wave throughout the septal mass Since under normal circumstances, the activation of the left septal surface precedes that of the right by 0.01 to 0 02 sec, when a slight delay in the transmission of this wave occurs in the left branch (approximately 0 01 to 0 02 sec) both sides of the septum are simultaneously activated and consequently no Q wave is recorded.

2 *Second degree* In these cases, there is a greater delay of the conduction of the stimulus in the left branch, which nevertheless continues to transmit the impulse at a much lower speed Thus, the beginning of the left septal activation is recorded with a delay of 0.04 sec and is preceded by the right septal forces. *Septal activation occurs, therefore, in an opposite direction to normal, although only partially so.* The activation of the interventricular septum begins over the right septal surface and proceeds *from right to left;* if the barrier is transposed, the two septal forces will meet one another 0.04 sec later. It can be seen, therefore, that most of the septal activation proceeds from right to left, although this does not occur throughout the entire activation process, at the end of this process, late septal forces play a role and are directed from left to right. In this type of block, the Q wave, representing the normal first septal vector, disappears; there also is a slurring of the upstroke of R over the left ventricular epicardium. This represents the initial inverted activation of the septum (from right to left) and coincides with the initial r wave in the left ventricular cavity

3 *Third degree (complete left bundle branch block)*. In this type, the left branch is completely interrupted and is functionally incapable of transmitting the excitation wave. *The right branch activates the entire septal mass in an opposite direction to normal, i e., from right to left.* Septal depolarization is a comparatively slow process and takes place at an average speed of 300 mm/sec, which is similar to that of the spread of activation in the myocardial fibers themselves. This alone, however, does not explain the great delay of activation on the left side of the septum as compared

with the right (approximately *0.07 to 0.08 sec*)

According to *Sodi Pallares* (1956), the inverted activation of the interventricular septum *is retarded* at ... ually there is a delay at the ba ... w. ... is ... in ... opposite direction to that normally ... finally, the third delay occurs upon arrival of the activation wave at the left septal surface, which *acts as a second* barrier These points of delay explain *both the widening* of the QRS complexes and the slurring and notching of its various *components* which are characteristic of the complete left bundle branch block In all degrees of left bundle branch block, notwithstanding the marked *alterations in septal activation (which is not only delayed but often completely inverted in direction)*, the activation of the *free wall* of the left ventricle remains unchanged, although it begins later than normal, because of the delay that occurs in the interventricular septum

It has not been possible to confirm the above-mentioned concept of these partial types of left ventricular conduction defect by the vectorcardiographic analysis of the incomplete types of left bundle branch block In cases with electrocardiographic signs suggestive of incomplete left bundle *branch block, the horizontal plane VCG has shown a counterclockwise rotation*

THE ELECTROCARDIOGRAM IN BUNDLE BRANCH BLOCK

The general characteristics of the bundle branch blocks consist of *widening of the QRS* complexes *with slurring and notching of its various waves, delay of the intrinsicoid deflection in leads corresponding to the homolateral ventricle, prolongation of electrical systole, and secondary T-wave changes* It is to be emphasized that in addition to the characteristic *contours of the* electrocardiogram, the practical diagnosis of right or left bundle branch block requires certain data for a *more precise recognition* of *those conduction* defects, such as a *supraventricular* pacemaker, a P-R interval above 0 12 sec, and a typical configuration in the precordial leads Thus, the *diagnosis* of bundle branch block *cannot* be made in the *presence of complete* AV block, on the other hand, a P-R interval below 0 12 sec with a widened QRS complex usually *corresponds to* the Wolff-Parkinson-White *syndrome. A* complete set of precordial leads usually *permits* a precise *identification* of the bundle branch involvement, which is often difficult *on* the basis of the standard leads alone, especially in cases *of left bundle branch block in vertical hearts*, or right bundle branch blocks in *horizontal* hearts.

All types of bundle branch block may be *permanent* or *intermittent, in* the latter group are included cases in which the conduction defect *is transient,* with normal and aberrant *QRS complexes recorded in the same tracing.*

In some instances, the *electrocardiogram* may show alternating complete and incomplete bundle branch block, a fact in favor of the general concept of the *incomplete types of* conduction defect.

Complete Right Bundle Branch Block. In right *bundle branch block*, the initial septal vectors are directed from left to right (as *in the normal heart)* and the main abnormality *occurs in the final vectors. The study of* the unipolar, epicardial, and intracavitary potentials in right bundle branch block has led to a better understanding of the changes *observed* in standard and precordial leads

Intracavitary leads in right bundle branch blocks *were recorded by* Sodi Pallares et al. *(1948b), in* dogs as well as in human beings, and the configurations obtained corresponded to those calculated by the vectors of cardiac activation. Thus, in the right ventricular cavity, rsR'S' *complexes were recorded,* whereas *in the left ventricle,* the tracing *was essentially a QS wave* with notching and slurring of the descending limb (Fig. 11-25).

An important point to remember is that a part of the free wall of the right ventricle *corresponding to the trabecular zone is very thin* and rarely exceeds 2 mm, *leads* V_2 *and* V_3, which usually *overlie this area,* record potentials closely *resembling those of the right* ventricular cavity. This configuration is generally rsR'S', which *is explained* by the direction and magnitude *of the main* vectors ... ndle branch ... reference to ... of the free wall of the right ventricle *corresponding to leads* V_1 and V_2, the configuration is rsR', *with a notching* of the upstroke of the R' wave This shows the great delay *in the intrinsicoid deflection* over the right ventricular activation which occurs in right bundle branch block

The r and s waves correspond to vectors *1 and* 2 and coincide with the two *initial intracavitary* deflections The initial portion of R' is due to the

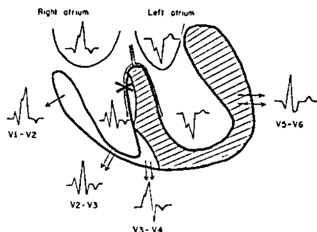


Fig. 11-25. Intracavitary and epicardial potentials in right bundle branch block.

third cardiac vector, which is the second septal vector This is demonstrated by the fact that the notching of the epicardial R′ is simultaneous with the peak of the intracavitary R′ (Fig. 11-23C, D). Finally, the peak of the epicardial R′ marks the arrival of the wave of excitation on the surface of the right ventricle and corresponds to the right intracavitary s wave. In other portions of the right ventricle corresponding to precordial leads V_3 and V_4, RS complexes are obtained with a notch on the ascending limb of the R wave This deflection is also partially due to low septal vectors located in the right portion of the septal mass, since this configuration cannot be explained on the basis of the above four vectors This has been emphasized by Sodi Pallares, who called attention to the fact that these R waves disappear in infarctions of the lower part of the septum

Over the epicardium of the left ventricle, qRS complexes are recorded, the initial negative deflection is due to septal activation from left to right, the R wave represents the activation of the free wall of the left ventricle (vector 2), and the S wave is generally widened and slurred, corresponding to vectors 3 and 4, which point away from the exploring electrode

In right bundle branch block, as shown above, the main abnormalities are those of the *late vectors*, which explains the slurring at the end of the QRS complexes in lead I and left precordial leads and the late R in aVR and in the right precordial leads, since the first vectors are directed from left to right, as in normal individuals, the q waves are present in lead II and over the left precordium, whereas the right precordial leads usually show an initial positive deflection.

On the basis of these data, the configuration of the various leads in right bundle branch block is easily understood

STANDARD LEADS. The QRS complexes show (Fig. 11-28A) notching and slurring with a duration of 0.12 sec or more, a widened S wave in lead I, usually smaller than the preceding R wave, is one of the main characteristics of this type of block; the q wave is usually present in this lead but may not be observed in certain cases. In lead III, the main deflection of the QRS complex varies according to cardiac rotation, it is negative in the horizontal hearts and positive in the vertical hearts. Several associated factors may change the configuration of the right bundle branch blocks in standard leads, particularly ventricular hypertrophy, myocardial disease, and the electrical position of the heart On the basis of the variations in configuration of the QRS complex in these leads, Bayley and Wilson et al. (1932) described several varieties of right bundle branch block which were subsequently thought to have different prognostic implications (Wilhus et al, 1941)

From a practical standpoint, the most common variety of right bundle branch block is the so-called *Wilson type of block* or *wide* S_1 *variety* It is characterized in lead I by a small initial q wave followed by a distinct, narrow R wave and a wide slurred S wave, with a positive T wave. In lead III, there is an rS complex or a deep Q wave with upright T in the horizontal heart, whereas in the vertical heart, the main QRS deflection is positive in lead III and is followed by a negative T wave. This variety of right bundle branch block is found in several types of heart disease, especially in chronic coronary insufficiency, but it may also occur in apparently normal individuals

The so-called *rare type of right bundle branch block* shows a small r in lead I (which may be absent in some cases), followed by a deep and wide S wave, while in lead III, the main QRS deflection is positive. The T wave in these leads is in the opposite direction of the QRS complex This type of right bundle branch block is often seen in right heart disease, suggesting the association of right bundle branch block with right ventricular hypertrophy.

A relatively rare variant of the Wilson type of right bundle branch block is the so-called *concordant inverted type*, in which wide S waves are present in the three standard leads (S_1, S_2, S_3)

Another type of right bundle branch block shows a wide, notched R wave in lead I, with or without an S wave and left axis deviation; the precordial leads are typical of right bundle branch block This type is not rarely encountered in cases of arteriosclerotic heart disease, but is especially common in Chagas' disease (Benchimol et al, 1954), where right bundle branch block is an exceedingly frequent finding However, vectorcardio-

graphic studies seem to indicate that these cases correspond to left bundle branch blocks associated with extensive septal and inferolateral infarctions The standard leads in right bundle branch block also show secondary changes of the repolarization process, with asymmetric T waves in the opposite direction of the major deflection of the QRS complex, thus, they are usually positive in lead I, in view of the marked widening of the S wave, and negative in lead III The electrical axis of the T wave (AT) is usually deviated to the left, as opposed to the right axis deviation of the QRS complex.

UNIPOLAR LIMB LEADS The configuration of aVL and aVF varies according to the electrical position of the heart, although in aVR there is always a late, slurred R wave (Fig 11-28A). This deflection is due to the late activation of the right ventricle from left to right, upwards and anteriorly (vector 4), in the direction of the right arm The QRS complexes are similar to those obtained in the right atrial cavity, whereas those of aVL and aVF resemble the left ventricular epicardial leads

PRECORDIAL LEADS In the right precordial leads (V_1 and V_2), the ventricular complexes are usually of the rsR' type with variations in the amplitude of the deflections from one case to another, involving particularly the first two waves of the QRS complex Occasionally, the S wave does not reach the base line and the configuration becomes rR' *The peak of the R' wave corresponds to the arrival of the wave of excitation over the right ventricular epicardial surface and is always delayed* Very often, there is a notch on the ascending limb of R' which marks the end of septal activation and the beginning of depolarization of the free wall of the right ventricle (Fig 11-23C, D), this was demonstrated by simultaneous recordings of precordial and right ventricular intracavitary leads

Since the beginning of septal activation is unchanged in right bundle branch block and is directed from left to right, the QRS complexes are almost always initially positive However, the absence of an initial r wave in V_1 does not necessarily represent an associated anteroseptal necrosis, it may be due to either a perpendicular direction of the first vector to lead V_1, or an enlarged right atrium which transmits its potential to lead V_1

With reference to ventricular repolarization, secondary inversion of the T wave is often seen, with a depressed S-T segment in leads V_1 and V_2

In the left precordial leads (V_5 and V_6), the QRS complexes are usually of the qRS type, similar to lead I, with a wide and slurred S wave (Fig 11-28A) In the absence of an associated left ventricular hypertrophy, there is no delay in the intrinsicoid deflection The T waves are generally positive, if they are negative, this suggests

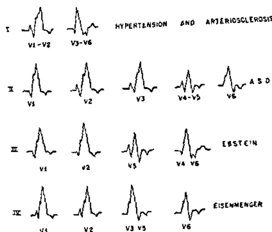


Fig. 11-26. Right bundle branch block in various types of heart disease (precordial leads).

myocardial ischemia or left ventricular hypertrophy.

In the intermediary points over the precordium (between leads V_1 and V_2), it is not unusual to record QRS complexes which resemble those of the right intracavitary leads (rsR'S'), probably corresponding to the thin trabecular zone of the free wall of the right ventricle In leads V_3 and V_4, an RS configuration is frequently obtained with a notch on the ascending limb of the R wave These waves are probably due to the low septal vectors pertaining to the right ventricular portion of the septum, as previously described (Fig. 11-25)

In the following types of heart disease with right bundle branch block, certain configurations of the precordial leads are often of diagnostic importance (Fig. 11-26):

1 In *arteriosclerotic* and *hypertensive heart disease* it is not unusual to record qRS complexes from leads V_3 to V_6, suggesting that the potentials of the hypertrophied left ventricle are transmitted to all leads which are to the left of V_3

2. In *atrial septal defect* (ASD), qR complexes are often obtained in lead V_1, because of right atrial enlargement, whereas the remaining precordial leads (V_2 to V_6) show right ventricular potentials, initially (V_2 and V_3) according the potential variations or the free wall, then those of the trabecular zone (V_4 and V_5), and finally those of the right side of the septum (V_6).

3. In *Ebstein's disease*, the potentials of the right atrium (qR) are recorded in leads V_3R, V_1, V_2 and occasionally extend to other precordial leads The left ventricular potentials

(qRS) are recorded in leads V_4 to V_6. Only occasionally are the right ventricular *potentials* obtained from the trabecular zone *in lead* V_3. Thus, in Ebstein's disease, the dominant electrocardiographic signs are those due to the right atrium and left ventricle, with a *limited* area of right ventricular complexes over the precordium.

4. In *Eisenmenger's syndrome*, leads V_3 *to* V_6 *reflect the potential variations of the lower* part of the septum, whereas leads V_1 and V_2 record *rsR' complexes* from the free wall of the right ventricle. Left ventricular *configurations* (qRS) are occasionally seen in lead VF.

Complete Left Bundle Branch Block. *When the left branch of the bundle of His is incapable of transmitting the cardiac stimulus, the entire septum is activated from right to left and the initial vectors become definitely abnormal. As a result, the q wave disappears in all leads which reflect the potentials of the left ventricle. In addition, there are an increased duration and a change in configuration of the QRS complexes, which become widened, slurred, and notched.*

These abnormalities can be attributed to the three main points of delay in the spread of the *stimulus* throughout the septal mass, as previously discussed with reference to cardiac activation in left bundle branch block.

A comparison of the unipolar epicardial configuration with the intracavitary leads is important in order to understand and interpret the standard and precordial leads. According to the experimental work of Sodi Pallares et al. (1950), in the intracavitary lead of the *left* ventricle, the form of the QRS complex varies from one point to another, in the lower part of the cavity, RS complexes are obtained, whereas the upper posterobasal portions show a qR configuration. The presence of a q wave in those leads is presumably due to the first *septal vector*, which is oriented from right to left, downwards, and slightly anteriorly; it is also possible that the lower part of the right aspect of the septum may contribute toward this deflection. This configuration is important for the diagnosis of infarcts involving the middle third of the septum, since in these cases, instead of RS complexes in the lower part of the left ventricular cavity, the tracing shows qR deflections resembling those of the posterobasal intraventricular leads. The S wave, which may be recorded in the cavity of the *left* ventricle, is probably due either to the activation of the upper part of the septum or to that of the free wall of the left ventricle.

In the cavity of the *right* ventricle, the configuration of left bundle branch block is essentially negative (QS), with notching and slurring of the QRS complexes.

Certain aspects of the epicardial leads in relation to the intracavitary potentials need further discussion (Fig. 11-27A). In the epicardial leads over the right ventricle, the R waves are often absent from V_1 to V_4, in view of the fact that the right-to-left septal vector is of great magnitude and neutralizes those of the free wall and the lower septal portion of the right ventricle. In the leads over the left ventricle (V_5 and V_6), the ascending limb of the R wave is probably due to the spread of the stimulus through the barrier, whereas the slurring of the "plateau" of the QRS complex corresponds to the activation of the septum from right to left; finally, the last peak of the

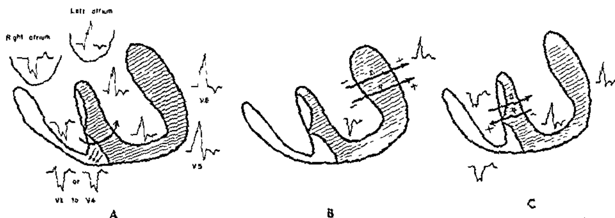


Fig. 11-27. A. Intracavitary and epicardial potentials in left bundle branch block. B. Ventricular repolarization in the normal heart. C. Ventricular repolarization in left bundle branch block.

R wave is due to the depolarization of the free wall of the *left ventricle*. Actually, it is not *known exactly where the septal activation ends* and that of the free wall of the left ventricle begins.

STANDARD LEADS. The *QRS complexes* are notched, slurred, and *widened, with a duration of* 0.12 sec or more (Fig. 11-28B). *There are no q or S waves in lead I*, and the mean electrical axis of the QRS complex (ÂQRS) is deviated to *the left from 0 to −75°. In rare cases*, the electric axis is *within normal limits, and under unusual* circumstances, a right axis deviation may be *present*.

The presence of a q wave in lead I would suggest a previous septal infarction, peri-infarctional *block, respiratory* variations of cardiac position, or *other factors, including right ventricular hyper*trophy.

The variations of *ÂQRS* in left bundle branch block are due *to several factors, such* as left ventricular hypertrophy, the location and extension of coexistent myocardial lesions, and especially the position of the heart in the chest. The *concordant* types and those with right axis deviation are generally found in *vertical hearts*.

The T waves are asymmetric and opposed to the major deflection of the QRS *complex, this is also observed with reference to the S-T segment*.

UNIPOLAR LIMB LEADS. The patterns obtained in these leads are essentially dependent upon the electrical position *of the heart*. Since left bundle branch block is mostly seen in horizontal hearts, lead aVL records left ventricular potentials and is similar to leads *I*, V_5, and V_6. *In some of these cases, a small q wave may be recorded in these leads in the absence of anteroseptal infarction. In lead aVF, the* ventricular complexes are of the *rS* or *QS* types, a fact which is *not due to myo*cardial *necrosis. Lead aVR* shows variable configurations (rS, QS, QR), according *to the position* of the QRS axis, and generally *resembles* the right atrial intracavitary lead.

In the unusual cases occurring in *vertical hearts*, aVF records left ventricular *potentials* and aVL faces *the right* ventricle, whereas aVR is *variable* and depends upon the degree of right axis deviation. *This* electrical position is *responsible for* patterns simulating *right bundle branch block* in the standard *leads, although* the *precordial* configurations *are typical and diagnostic*.

PRECORDIAL LEADS. In leads V_5 and V_6 corresponding to the *left ventricle*, essentially positive QRS complexes are obtained with an *initial, slurred* R wave of variable *amplitude (Fig. 11-28B)*. Following this deflection, there is *always a notched* plateau which extends to *the peak of a* rapid and *delayed intrinsicoid* deflection; in certain cases, these complexes *assume* an M-shaped configuration. There is, as yet, no *complete agreement as to the correct interpretation of the pattern*.

It is to be emphasized that in hearts with *marked clockwise rotation*, these QRS complexes are *observed only* in lead V_7 (or farther to the left), which may suggest an associated *right* ventricular enlargement. The T waves *are negative*, with an S-T segment depression and an upward *concavity of the S-T segment*; these repolarization changes are secondary *to the QRS abnormality*.

In *leads* over the right ventricle (V_1 and V_2), *the tracing does not* show remarkable *changes*, as it begins with a small r wave and ends with a *wide and* deep *S wave. The persistence* of the initial r wave *in the left bundle branch block, in* the presence of an inverted septal activation, is probably *explained* by early *activation of* the free wall of the right ventricle, in addition to that of the lower portions of the septum pertaining to *this ventricle. Very often, however*, this small *r wave disappears*, and *QS* complexes *are recorded* in the right precordial leads, suggesting *the presence* of anteroseptal infarction. In these cases, the negativity *is explained by a neutralization* of the *lower* septal *vectors* and *those of the free wall by the more powerful* septal forces directed from right to left. The T waves *are positive* in these leads, with elevated S-T segments.

Ventricular Repolarization in Left Bundle Branch Block. Under normal *circumstances*, the repolarization *process of the free wall of the left ventricle dominates* that of the interventricular septum, and explains the negative T wave in the ventricular *cavity with an upright* deflection over the epicardial surface. This is because, in *man*, repolarization proceeds in an opposite direction to that *of depolarization* (Fig. 11-27C and D). *In left bundle* branch block, septal repolarization is greater than that of the free wall and is directed from right to left, although the *vector is conventionally represented in the* opposite direction. This explains the negative T wave both in the cavity and over the left ventricular *epicardium*. Consequently, *septal repolarization* is *mainly* responsible for *the T-wave changes* in left bundle branch block.

INCOMPLETE BUNDLE BRANCH BLOCK

The *concept of "incomplete"* bundle branch block *presupposes* a delay in conduction through one of the branches of the *His bundle*, although the *excitation wave* is not entirely

arrested as in the "complete" types of block. Thus, the activation of each ventricle in the incomplete bundle branch blocks proceeds through its corresponding branch, though with a variable degree of delay.

This interpretation was accepted following the investigations of Wilson and Herrmann, which were later confirmed and extended by Sodi Pallares (1950), in addition to the clinical observation of tracings similar to those experimentally obtained

The fact that both clinically and experimentally, continuous tracings were obtained showing QRS complexes intermediate in configuration between normal records and complete bundle branch block (Fig 11-32A) seems to confirm the actual existence of incomplete bundle branch block, which has been such a controversial subject among the various investigators.

From the morphologic standpoint, these tracings resemble complete bundle branch block, although the duration of the QRS complexes is less than 0.12 sec (usually between 0.10 and 0.12 sec). However, Sodi Pallares attaches greater importance to the morphologic

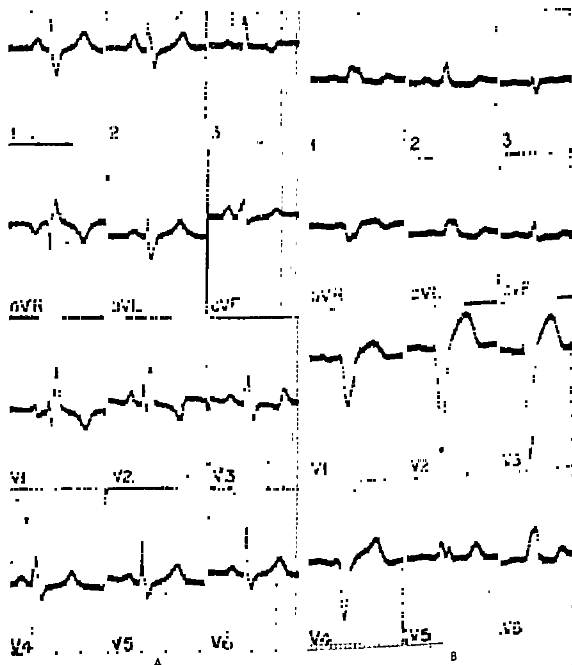


Fig. 11-28. A. Complete right bundle branch block in a 29-year-old patient with interatrial septal defect B. Complete left bundle branch block in a 60-year-old patient with arteriosclerotic heart disease.

criteria than to the delay of the intrinsicoid deflection, accepting as incomplete bundle branch blocks even cases with a *normal* QRS duration (*less than* 0.10 sec).

Incomplete Right Bundle Branch Block. This type includes electrocardiograms with an rsR' configuration in the right precordial leads, with variable amplitudes of the individual deflections, and a total duration of the QRS complexes below 0.12 sec. Although the intrinsicoid deflection is inscribed with a delay of 0.04 to 0.05 sec, the marked delay observed in incomplete right bundle branch block *is not seen in these cases. In the standard leads,* the tracing *may be normal,* although there often is a slurred S wave in lead I and a late wide R wave in lead III.

This type of electrocardiogram is frequently observed in normal individuals, although it is especially common in diseases affecting the right heart (atrial septal defect, tricuspid insufficiency, etc.). Although Sodi Pallares et al. (1950) consider this configuration as due always to a right bundle branch conduction defect, Kossmann et al. (1950) admit the possibility of a late activation of the crista supraventricularis of the right ventricle, both in normal individuals and in some persons with right ventricular hypertrophy.

From a practical standpoint, it is obvious that not all tracings with this configuration actually represent incomplete right bundle branch block. However, it is extremely difficult to distinguish the true incomplete right bundle branch block from similar tracings which correspond to normal variants, or those due to right ventricular hypertrophy, although several criteria have been suggested to differentiate these conditions. The most important practical contribution to this problem has been that of *vectorcardiography* in clarifying certain aspects of the rSR' configuration in V_1.

Incomplete Left Bundle Branch Block (Fig. 11-24). The *first-degree left bundle branch block* is characterized by an absence of q waves in leads V_5 and V_6, which is not in itself sufficiently diagnostic, since this may occur in normal individuals with vertical heart and a clockwise rotation. However, the presence of an initial slurring of the R wave in these leads is of greater diagnostic importance, since it represents bilateral septal forces which neutralize each other. The T waves are either normal or slightly decreased in amplitude.

In *second-degree left bundle branch block*, septal activation is partly inverted, the majority of the septal mass being activated from right to left. Only a small portion of the left side of the septum is activated by late forces directed from left to right. In these cases, Q waves are absent in leads V_5 and V_6 and there is a slurring of the entire upstroke of the R wave. The duration of the QRS interval is slightly greater than that of first-degree bundle branch block, and the T wave becomes negative because of the inverted direction of septal repolarization (Fig. 11-32B).

In contrast to the incomplete right bundle branch block, which may occur in normal hearts, in the majority of cases, incomplete left bundle branch block denotes organic heart disease with left ventricular hypertrophy. The occurre [illegible] and in [illegible] nating [illegible] important evidence in favor of the incomplete bundle branch block concept, which is still denied by some authors.

BUNDLE BRANCH BLOCK AND VENTRICULAR HYPERTROPHY

The configuration of right bundle branch block, especially of the incomplete type, is often seen in certain types of right heart disease, such as atrial septal defects, tricuspid insufficiency, etc., and has been described by Cabrera and Monroy as evidence of *diastolic overload* of the right ventricle. Although this is true in most cases, it should be emphasized that similar electrocardiograms may be observed in normal hearts and in cases of true right bundle branch block. The distinction between these three conditions is difficult from an electrocardiographic standpoint, and it is often necessary to base the interpretation upon clinical data and on other abnormalities of the tracing (P pulmonale, Lewis index, right axis deviation, etc.). *Vectorcardiography* is of great help, because the orientation of the loop in the horizontal plane is frequently diagnostic and differs in right ventricular hypertrophy from that in normal hearts and in right bundle branch block.

It is well known that left bundle branch block usually coexists with left ventricular hypertrophy. According to most authors, the latter is practically inferred in the presence of this type of conduction defect; however, there are

a few exceptions to this rule, such as the case shown in Fig. 11-24B.

In the presence of associated bundle branch block, the classical electrocardiographic criteria for the diagnosis of ventricular hypertrophy may not apply, because of the altered pathways of ventricular activation. In such instances, the recognition of ventricular overload may be extremely difficult.

A review of the criteria proposed by a number of authors, which so far have been accepted, has shown that they cannot be used in many cases.

Many of these patterns appear in *experimental blocks*, and occasionally in a variety of clinical cases, in which the diagnosis of coexistent ventricular hypertrophy cannot be made unequivocally. On the other hand, certain cases of *transient bundle branch block* with suggestive evidence of associated hypertrophy have not exhibited any of the diagnostic criteria of ventricular overload following the restoration of normal conduction.

At present, it appears that the best criteria for the diagnosis of ventricular hypertrophy associated with bundle branch block are the following.

1 *Diagnosis of right ventricular hypertrophy in the presence of right bundle branch block*

a. Signs of right atrial enlargement

b. Right axis deviation exceeding +120°

c. Presence of RR′ in leads to the left of V_3 (this is considered as evidence of right ventricular dilatation)

d. Deeply inverted T waves in V_1, V_2, and V_3

Although, from a statistical standpoint, deep S waves in leads I, V_5, and V_6, or an R′ exceeding 10 mm in V_1, occur more frequently in cases of associated right ventricular hypertrophy, these signs may also make an appearance in many cases of isolated right bundle branch block.

2. *Diagnosis of left ventricular hypertrophy in the presence of right bundle branch block*

a. Signs of left atrial enlargement (in the absence of mitral stenosis)

b. R waves of high voltage and a delayed intrinsicoid deflection in V_5 and V_6 (0.05 sec)

c. Deep S wave preceding an R′ in V_1 and V_2

d. QRS axis deviated upwards and to the left in the frontal plane

e. Presence of q waves in leads I, V_5, and V_6

Other minor signs, which may be useful in some cases, are the early transition in the precordial leads and the presence of T-wave inversion in leads V_5 and V_6

3. *Diagnosis of left ventricular hypertrophy in the presence of left bundle branch block*

As previously stated, the presence of left bundle branch block in itself is considered evidence of associated left ventricular hypertrophy in view of the high statistical incidence (approximately 95 per cent) of left ventricular enlargement in cases of left bundle branch block. Nevertheless, the following signs are highly suggestive of left ventricular hypertrophy in the presence of left bundle branch block:

a. Sokolow-Lyon index above 35 mm

b. White-Bock index above +18 mm

c. Marked left axis deviation of the QRS complex, with right axis deviation of the T wave

d. Tall R waves in the left precordial leads with a tendency to the disappearance of the "plateau"

e. Signs of left atrial enlargement (an indirect sign, although one of the most important diagnostic criteria of associated left ventricular hypertrophy)

Under these circumstances, it is very difficult to identify right ventricular hypertrophy for several reasons, including the fact that these cases usually exhibit biventricular hypertrophy associated with left bundle branch block.

However, vertical electrical position of the heart, clockwise rotation, and leftward displacement of the transitional zone in precordial leads with S waves in V_6 and V_7 are highly suggestive of coexistent right ventricular hypertrophy (Laham, 1951, 1952).

From a *vectorcardiographic* standpoint, the association of right ventricular hypertrophy and right bundle branch block has been described (Burch et al., 1953, Wolff et al., 1953) as showing a displacement of the QRS loop anteriorly and to the right and as maintaining the classical VCG characteristics of right bundle branch block (delayed terminal appendage) [Fig. 11-36(2)]

Left ventricular hypertrophy in right bundle branch block displaces the loop so that it as-

rather a *more superior* orientation as compared with its position in uncomplicated right bundle branch block (Grishman and Scherlis, 1952, Burch et al., 1953, Massie and Walsh, 1960).

An interesting type of left ventricular hypertrophy with *terminal delay in intraventricular* conduction has *been* described by Grishman and Scherlis (1952). *In* these cases, the ECG displays *a widened* QRS complex, with wide, *slurred S waves in* V_6, marked left axis deviation, and secondary *S-T segment and T-wave* changes.

The VCG in *these cases shows the* typical *signs of left ventricular hypertrophy,* with a *delay in the terminal* segment of the afferent portion of the *QRS loop,* which is oriented to *the right, posteriorly,* and superiorly.

INTERMITTENT BUNDLE BRANCH BLOCK

Experimentally, a complete bundle branch *block* pattern may be *obtained* by direct percussion of one of the branches *of* the bundle of His (this is more easily *obtained* in the right *bundle branch), and serial changes of* the tracing are *recorded. It is interesting to note then that as the conduction* defect improves, the degree of *block progressively* decreases until *normal conduction is* finally restored. It is conceivable, therefore, that in the *presence of an* organic lesion of one of the *branches* of the *bundle* of His, the *occurrence of* an attack of tachycardia, or any other *aggravating* factor of *the* conduction defect, *may* lead to a transient *block of* the impulse through the damaged bundle branch. Thus, intermittent bundle branch blocks are *probably more common than they appear to be statistically,* and would probably be more *frequently* recorded if *serial* tracings were *obtained in* the initial stages of the organic bundle branch lesions. Nevertheless, numerous *cases* of *transient bundle* branch block have been published in the literature (Bentchumol, 1944, 1945), *demonstrating* that *this is not a rare finding in clinical cases*.

It was *thought* at first that this represented a purely *functional disturbance,* however, it is now *considered* to be *due to lesion of the* conduction tissues, frequently denoting *advanced* cardiac disease. The *majority* of the so-called "functional" bundle branch blocks is observed in the course of supraventricular tachycardia or atrial flutter or fibrillation. Although *some* patients with this type of block do not appear to suffer from any cardiac disease, *it is* difficult to rule out minor *lesions of the* conduction tissues leading to *fatigue of* the bundle branch with a decrease *in its conduction* capacity in the presence *of a functional strain.* Many factors have been *described* as capable of precipitating *these* types of block. Thus, changes *of vagal tone* or of heart rate, hypoxia, heart failure, toxic processes, etc., have been considered.

Although *changes* in vagal tone may indirectly influence intraventricular conduction, it appears that this increased tone is not *directly* ...sible for the prolonged inhibition of con- [illegible]

factor, have been described (*Vessell,* 1951). There was a critical *rate for the appearance of* block, and this *often disappeared following a* slight decrease *of rate. In other instances, the* bundle *branch block appears on effort or following some* factor which temporarily overloads the heart in the presence of advanced *pathologic* changes (*usually due to* coronary arteriosclerosis).

In these cases, the different involvement *of* the two branches *leads to a difference of their refractory periods.* However, *a normal* intraventricular *conduction* is still compatible with a permanent increase in the refractory period predominating in one of the branches of the *bundle of His.* The *conduction* defect only appears *following the influence* of certain *factors, which increase the refractory period or inhibit conduction completely.*

Cases have *been described in which bundle* branch *block appeared in the course of heart* failure and *disappeared as soon as cardiac* compensation was obtained. *Other* instances



Fig. 11-29. Electrocardiogram of a 65-year-old male with complete right bundle branch block and anterolateral infarction: deep Q waves are recorded in left precordial leads, with the typical right bundle branch configuration maintained in leads V_1 *and* V_2.

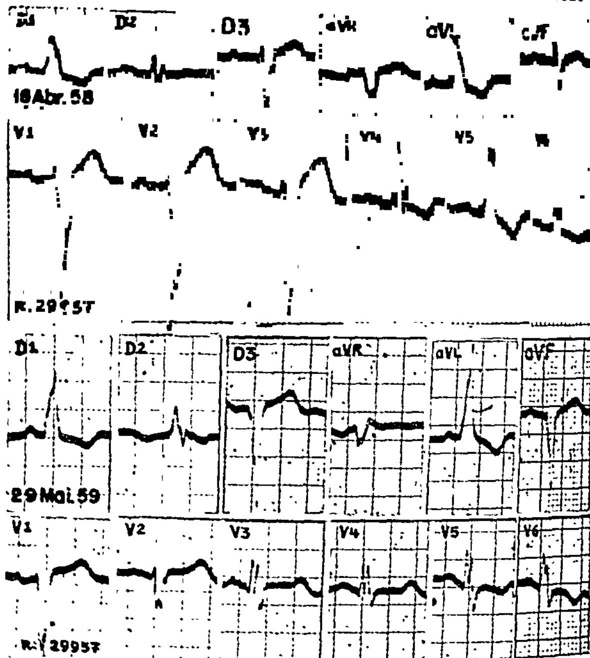


Fig. 11-30. Electrocardiogram of a 60-year-old patient with arteriosclerotic heart disease, showing complete left bundle branch block in the upper tracing. Bilateral internal thoracic artery ligation was performed for the relief of angina pectoris in June, 1958. In May, 1959, the patient sustained an acute coronary thrombosis; the ECG recorded 4 weeks later (lower tracing), shows deep S waves not previously present in leads V_5 and V_6, probably because of the transmission of the left intracavity potential (RS) to the exploring electrode through the area of necrosis.

have been reported in the course of *digitalis intoxication* (Benchimol, 1944) It is possible that these cases may be due to a vagal influence, although it is believed by most authors that a direct toxic effect on the conduction tissue, such as occurs in cases of *myocarditis*, is probably responsible.

In clinical practice, when an intermittent type of bundle branch block is recorded, it often appears or disappears following physical effort, amyl nitrite inhalation, or atropine injection.

Vagal stimulation obtained by ocular compression may cause the block to disappear, as in Fig 11-31. This is not a direct vagal effect upon the bundle branch, but rather an indirect

of the bundle branch system.

These types of intermittent bundle branch

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a number of transitional complexes of ... plete bundle branch block are recorded preceding the final appearance of the complete type of conduction defect. These tracings, occasionally recorded clinically (Fig. 11-32A), seem to confirm the concept of incomplete bundle branch block as previously described. Occasionally, normal conduction alternates with bundle branch block, either regularly (2:1; 3:1; 3:2, etc.) or irregularly, without any ap... Such tracings are usually desig-

...

secondary changes in ventricular repo...

BUNDLE BRANCH BLOCK AND MYOCARDIAL INFARCTION

The association of *bundle branch* block with *myocardial* infarction is not rare, although certain types of block may obscure the electro-... ...ognition of infarction. The

...

an associated infarction is not difficult to determine. This has been shown experimentally in dogs by cutting the right bundle branch and ligating the anterior descending branch of the left coronary artery. The tracings obtained in human beings are essentially similar to those of

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cated with Q or QS waves due to transmission of the initial negativity of the left ventricular cavity to the epicardial surface over the region of the infarct. This is because in right bundle branch block, there is no change in the initial

...

terior or posterior wall, is transmitted to the epicardial surface. *In anterior infarcts*, the diagnosis is based upon abnormal Q waves in precordial leads. In *anteroseptal lesions*, these deflections are seen in leads V_1 to V_4 and the rsR' configuration is changed to QR with an increased duration of the Q wave (Fig. 11-33C). *In anterolateral infarctions*, the abnormal Q waves are recorded in the left precordial leads, and often in leads I and aVL (Fig. 11-29). Finally, in *posterior infarctions*, the diagnosis is based upon abnormal Q waves in leads II, III, and aVF, in addition to the characteristic right bundle branch block pattern in precordial leads. As for the evidence of injury and *ischemia*, they are important *diagnostically only* duri... ...course of infarction and, in the cour... since ... may show S-T–segment changes and T-wave abnormalities in the absence of infarction.

Sodi Pallares et al. (1948b), basing their con-... ...on modern concepts of ventricular

...

according to the site of necrosis (in the ... in the free walls of the ventricles). These studies have shown that abnormal Q waves in leads V_1 and V_2 *denote an infarct of the middle third of the septum*, whereas similar deflections in V_3 and V_4 indicate *low septal infarctions*. Deep Q waves in leads V_5 and V_6 are *characteristic signs of involvement of the free wall of the left ventricle*. When the infarct is located in *the free wall of the right ventricle or in the upper part of the septum*, there are no definite electrocardiographic signs that can be considered *diagnostically significant*. Some types of infarction included in this classification correspond to a combination of those previously described.

It should be *emphasized* that cases of right bundle branch block with *right atrial dilatation* often exhibit in leads V_1 and V_2 a qR configuration with a delayed *intrinsicoid* deflection, which *may lead to the erroneous diagnosis of right bundle branch block complicated by anteroseptal infarction*. The differential diagnosis *is established by the clinical data, by the progressive ST-T changes, and possibly by the presence or absence of Q waves in left precordial leads, since in cases of midseptal infarction the disappearance of the initial septal vector results in the absence of Q waves in left precordial leads.*

In the presence of left bundle branch block, the electrocardiogram seldom shows signs diagnostic of myocardial necrosis. This is explained by the fact that in left bundle branch block, the *initial vectors of ventricular activation are fundamentally* altered in direction and the *septum is depolarized in a* direction opposite *to the normal*, i.e., *from right to left*, causing an abnormal, initial positivity in the left ventricular *cavity*. Thus, *it is impossible to diagnose a necrosis of the free wall of the left ventricle because the cavity* potentials are transmitted to the *epicardial surface through* the "electrical window" and r waves are re-

D1

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V

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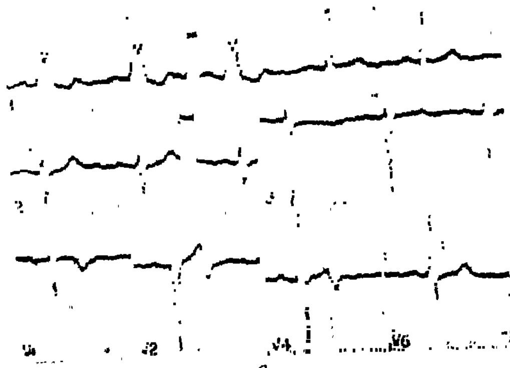
V5

Fig. 11-31. Electrocardiogram of a 67-year-old female with hypertensive and arteriosclerotic heart disease and angina pectoris of 2 years' duration. Note the initial complexes in each lead showing a normal intraventricular conduction This was obtained by a slight slowing of the cardiac rate as a result of ocular compression. The last QRS complexes in every lead exhibit a configuration of complete left bundle branch block In lead II, ventricular premature beats with a bigeminal rhythm are recorded.

corded instead of the typical Q waves which denote infarction. However, in the early stages of the coronary attack, the diagnosis of myocardial infarction associated with left bundle branch block may be suggested by ST-T and T-wave changes due to injury and ischemia, especially in cases that have a suggestive clinical history and in the presence of serial tracings.

When the infarct involves the *septal mass*, the initial negativity of the right ventricular cavity is transmitted to the left and is recorded through the infarcted area in left precordial leads, and occasionally in lead I. Thus, the presence of a Q wave in leads I, V_5, and V_6 in a case of left bundle branch block usually denotes an associated *septal infarction* (Fig 11-33D). The observation of RS complexes in leads V_7 and V_6 was suggested as a sign of *lateral wall infarction* in cases of left bundle branch block because of the recording of left intracavitary potential (RS) over the epicardial surface of the left ventricle through the area of myocardial necrosis (Fig. 11-30). It must be emphasized, however, that this configuration may also be recorded at the transitional zone if the latter is displaced to the left, as in a horizontal heart with a clockwise rotation.

It should be emphasized that Q waves may be present in leads I, V_7, and V_6 in cases of left bundle branch block without myocardial infarction. There are several possible interpretations for these initial negative deflections. (1) recording of left atrial potentials in horizontal hearts with marked clockwise rotation; (2) associated right



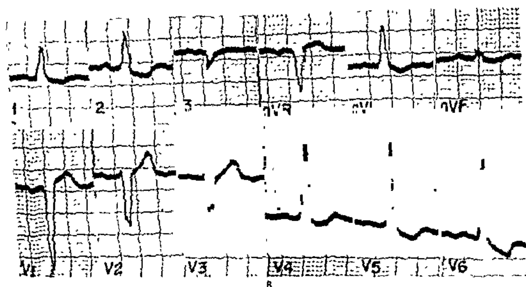


Fig 11-32 A *Left* bundle branch block Note in lead I a transitional complex with the configuration of incomplete left bundle branch block, followed by a QRS complex with normal intraventricular conduction (the last complex in lead I). In the remaining leads the ECG shows incomplete left bundle branch block. B Second-degree incomplete left bundle branch block in a 65-year-old patient with hypertensive and arteriosclerotic heart disease

ventricular hypertrophy; (3) right intraventricular conduction defect (Laham, 1952).

Certain cases of left bundle branch block show Q waves in leads I, V_5, and V_6 *in the* absence of myocardial infarction. This is because of one of the following possibilities: (1) recording of left atrial potentials over the *precordium in* horizontal hearts with marked clockwise rotation; (2) associated right ventricular hypertrophy; or (3) right intraventricular conduction defects.

Cabrera and Friedland (1953) called attention to the importance of a late notching of *the S or QS* wave in leads V_3 and V_4 as a *strong* indication of myocardial necrosis in the

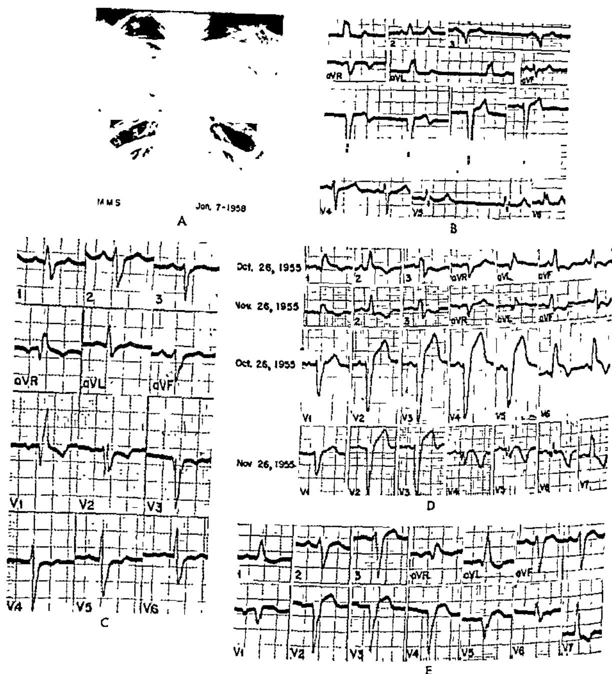


Fig. 11-33. A. Complete left bundle branch block in a 42-year-old patient who was asymptomatic and showed a normal heart size on roentgenologic examination B. Right bundle branch block and anteroseptal infarction C in a 45-year-old patient. D Complete left bundle branch block and anterior wall infarction with septal involvement, recorded during the acute and subacute stages of coronary occlusion. Observe ST-T changes and the deep Q waves in leads I, aVL, and V_6 indicating myocardial necrosis E Left bundle branch block and anterior wall infarction showing a late notch on the ascending limb of the S waves in leads V_2 to V_4. This case had autopsy confirmation.

presence of left bundle branch block (Fig. 11-33E).

Sodi Pallares et al. (1957) described eight varieties of infarction complicated by bundle branch block, which could be distinguished electrocardiographically on the basis of the modern concepts of ventricular activation and the identification of the intracavitary potentials. It was shown by these authors th[illegible] involvemen[illegible] block, could be sugge[illegible] tary potentials (RS) in precordial leads V_5 and [illegible] possible to [illegible] ment and in cases with extension into the [illegible] wall of the left ventricle.

Most pathologic studies have confirmed the electrocardiographic criteria for the diagnosis of myocardial infarction complicated by left bundle branch block.

THE VECTORCARDIOGRAM IN *BUNDLE BRANCH* BLOCK

Vectorcardiography has unquestionably played an important role in the better understanding of many obscure aspects of the ECG, particularly with reference to the intraventricular conduction defects.

Nevertheless, the subject of conduction defects has not yet been completely clarified, and there are still many controversial opinions regarding electrogenesis and the correct interpretation of many ECG tracings, as well as VCG loops. Adequate experimental data, in addition to electrovectorcardiographic correlation, are still lacking. Lately, however, important contributions have been published in the literature on this subject, and many problems have appeared requiring future investigation.

The VCG *is very useful* in the diagnosis of the more advanced forms of bundle branch block. Interpretation of the lesser degrees of these conduction defects is still controversial, and, at present, it is difficult to distinguish certain cases of ventricular hypertrophy from the so-called incomplete types of bundle branch block.

As previously mentioned, the electrocardiographic diagnosis of bundle branch block is based upon certain findings, such as atrioventricular conduction, abnormal slurring and notching of the QRS complexes, and a late R wave *in the unipolar leads facing the ventricle* on the side of the blocked bundle branch.

Atrioventricular conduction cannot be demonstrated in the VCG, *it is necessary to record* the ECG for this purpose. With reference to notching and slurring, the VCG is a more adequate tracing, since it distinguishes the true from the false *types of slurring*. *True slurring* is due to a slow inscription of the spatial vectors, and it is observed in the various planes, the *false types of slurring* result from the perpendicularity of certain portions of the VCG loop in relation to one of the planes, and are therefore limited to this *plane*.

Finally, the late R wave corresponding to the ventricle with delayed activation is shown in the VCG by a loop which points *toward this* ventricle. *As a rule, the main* vectorcardiographic features of bundle branch block are the slow inscription of certain portions of the loop, the direction of *the initial part of the* loop, and *frequently the type of rotation* in the horizontal plane (Grishman and Scherlis, 1952).

In Complete Left Bundle Branch Block. The *main VCG features* of complete left bundle branch block are as follows (Fig. 11-34):

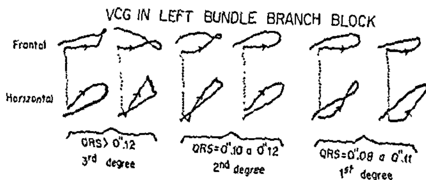


Fig. 11-34.

1. Changes in the spatial QRS loop. In the *horizontal plane,* the initial portion of the loop (Q loop) decreases, and is slowly inscribed, oriented usually forward and slightly to the left; in some cases, however, it is directed posteriorly and to the left, and very rarely anteriorly and slightly to the right. Whatever its initial direction, the QRS loop, sometimes after a sharp angulation, is rapidly inscribed posteriorly and to the left (R loop) with a clockwise rotation, which is the main VCG feature of this type of block.

The long axis of the loop usually lies between −30 and −60° in the horizontal plane. In the afferent limb, or more frequently in its middle portion, there is evidence of conduction delay, as shown by the closer proximity of the time markings. At this point, there is an irregularity of the loop, constituting a "plateau," the duration of which is proportional to the degree of block (Fig. 11-35).

Occasionally, the VCG in the horizontal plane is characterized by a "figure-8" type of rotation, with an initial counterclockwise direction followed by a clockwise inscription; in these cases, the Q loop is usually directed anteriorly and to the left.

The QRS sÊ usually fails to close prior to the inscription of the T sÊ loop, this is because it does not return to its point of origin, so that the J point is deviated to the right and anteriorly, resulting in an ST vector pointing in the same direction.

In the *frontal plane,* the QRS sÊ loop of the VCG is inscribed counterclockwise (with very rare exceptions), to the left, and superiorly. The loop is usually open, with an ST vector pointing downward and to the right.

In the *sagittal plane,* it is important to note the clockwise rotation of the loop, with its main axis pointing posteriorly and slightly superiorly or inferiorly. The loop fails to close as in the other planes, with an ST vector pointing anteriorly and slightly inferiorly.

2. Spatial T Loop (T sÊ). The T sÊ loop is usually oriented opposite the QRS sÊ loop, to the right, anteriorly and superiorly or inferiorly.

In Incomplete Left Bundle Branch Block. The vectorcardiographic criteria of incomplete left bundle branch block are much less precise

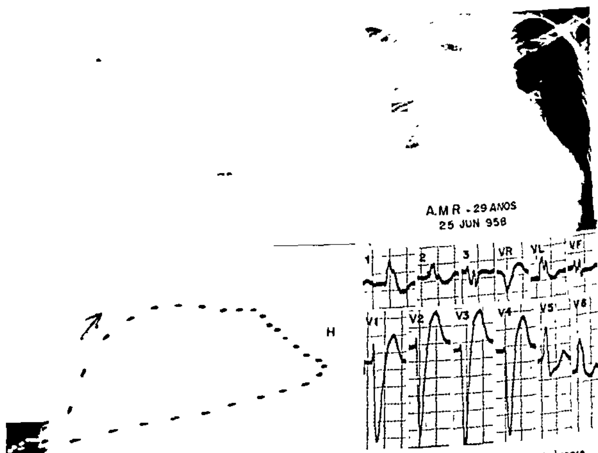
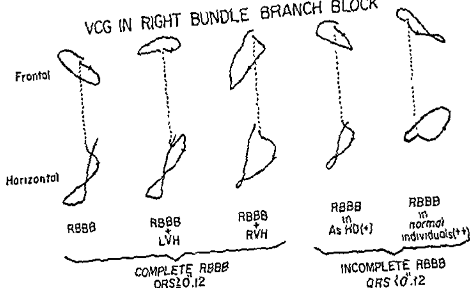


Fig. 11-35. Complete left bundle branch block in a 29-year-old male with Chagas' heart disease. The VCG shows the typical clockwise rotation in the horizontal plane with a delay in the middle portion of the loop.



\+ Arteriosclerotic heart disease
\++ This type of loop with QRS duration > 0".12 may complete RBBB and is often observed in chronic Chagas' heart disease

Fig. 11-36.

than those of the complete type. Very often, the VCG in incomplete left bundle branch block is similar in configuration to that of complete left bundle branch block, with the exception of its duration (less than 12 sec) and the lesser degree of slowing observed in the middle portion of the loop (first- and second-degree left bundle branch block) (Fig 11-34).

In certain instances, the slowing of the middle portion does not occur, but the loop is inscribed in a clockwise direction in the horizontal plane, this is an important distinguishing feature from simple left ventricular hypertrophy.

The QRS sE loop in the horizontal plane is *frequently inscribed to the left and posteriorly,* [illegible]

[illegible] portion or not. In these cases, the loop has a characteristic figure-8 type of configuration with a *slow inscription of its initial portions,* with or without an additional delay in the middle portion of the loop

Finally, in certain instances of incomplete left bundle branch block, the middle portion of the *horizontal QRS loop* shows either a slight slurring or a *counterclockwise rotation,* although a certain delay in the initial portion of the loop is observed, it is difficult to distinguish these types of VCG from those of left ventricular hypertrophy.

In Right Bundle Branch Block. *The initial portion of the* QRS sE loop is normally inscribed, i.e., to the right and anteriorly, since the initial vectors of ventricular activation remain unchanged in this type of conduction defect. The most important feature of the loop is its *terminal* portion, which is *slowly inscribed,* with an *irregular contour constituting* an appendage which in the horizontal plane is directed anteriorly and to the right (Fig 11-36) The general aspect of the loop varies in form and direction.

Two main types have been pointed out One was described by Grishman et al. (1938), with a QRS sE loop inscribed to the left and posteriorly and a counterclockwise rotation in the horizontal plane followed by a delayed terminal appendage (Fig. 11-36(1)). These loops correspond to the ECGs of the so-called *atypical forms of right bundle branch block,* and are often found in *chronic Chagas' heart disease,* AV communis, and other cardiac *conditions.* A second type of VCG in right bundle branch block has been emphasized by Cabrera et al. (1958), with the QRS sE loop in the horizontal plane *showing* an initial clockwise rotation,

followed by a counterclockwise inscription, and a preterminal delay often resulting in a figure-8 configuration [Fig. 11-36(2)]. This type is often seen in coronary heart disease.

The T loop is usually opposed to the delayed terminal appendage, and its abnormalities are less conspicuous than those of left bundle branch block. The vectorcardiographic distinction between *complete* and *incomplete right bundle branch block* is made solely on the basis of the duration of inscription, since there are no significant differences in configuration of the respective VCG loops.

The VCG has been found to be the most useful in distinguishing incomplete right bundle branch block from other tracings with an rsR' configuration in lead V_1, which correspond to either normal hearts or slight degrees of right ventricular hypertrophy.

ETIOLOGY

Coronary heart disease is undoubtedly the main cause of bundle branch block, either as an isolated factor or in association with arterial hypertension. One of the branches may be damaged by an *acute infarction*, followed by fibrosis, or by a slow and progressive *ischemia* due to chronic coronary insufficiency.

Bundle branch blocks may be found in the absence of any type of apparent organic heart disease; this is much more common in right than in left bundle branch block.

Left bundle branch blocks occur mostly in hypertensive or arteriosclerotic heart disease and in aortic valvular disease, especially in *calcific aortic stenosis* and in *syphilitic aortic insufficiency*. Less common causes are classified in Table 11-2.

Right bundle branch blocks are observed in normal persons and in a variety of organic heart diseases, and are thus commonly found in clinical practice.

In normal individuals, right bundle branch block is usually of the incomplete type, decreasing during the Valsalva maneuver and increasing during the Muller maneuver. The elec-

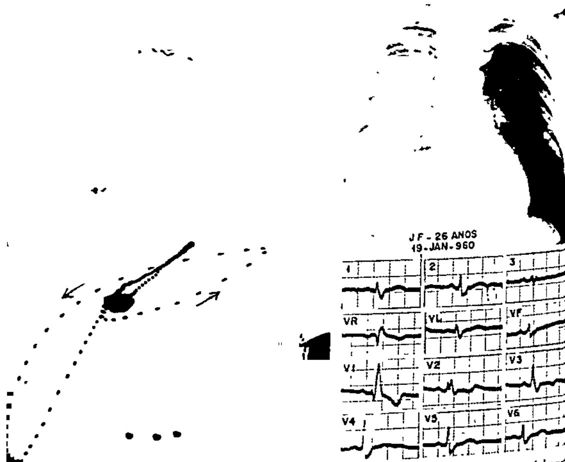


Fig 11-36(1). Complete right bundle branch block in a 26-year-old patient with Chagas' heart disease. The mean spatial QRS axis is at −150°. The VCG shows a counterclockwise rotation in the horizontal plane, with a terminal delayed appendage pointing rightward and anteriorly.

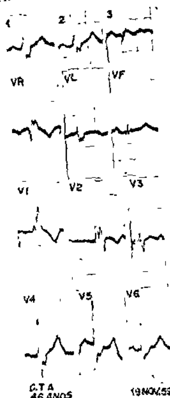


Fig 11-36(2). Right bundle branch block with ÂQRS at 180° in a 46-year-old patient. The VCG displays an initial clockwise rotation of the loop in the horizontal plane, followed by a counterclockwise rotation and a delay in the terminal portion

trocardiographic and *vectorcardiographic* features are usually similar to those found in pectus excavatus and in certain *atrial septal defects* without pulmonary hypertension

In younger patients, the main causes of right bundle branch block are *congenital heart disease*, *rheumatic heart disease*, and *Chagas' disease*.

With reference to rheumatic heart disease, right bundle branch block is usually found in the presence of mitral and tricuspid lesions. In these instances, P-wave changes diagnostic of biauricular enlargement are *usually present*, or atrial fibrillation, in addition to other characteristic changes of rheumatic heart disease.

In *pure mitral stenosis*, which exhibits a double-peaked R wave in V_1, there is usually *a moderate* degree of right ventricular enlargement.

In many Latin American countries, a common cause of right bundle branch block is

a complete type of right bundle branch block, with left axis deviation as a very common finding [Fig. 11-36(3)]. In serial tracings, other electrocardiographic abnormalities are often associated, such as ventricular premature beats and various types of AV block.

In congenital heart disease, right bundle branch block is frequently recorded (Table 11-3), especially in *atrial septal defects*, either as an isolated finding or associated with other cardiac malformations.

In isolated atrial septal defects, according to most authors, right bundle branch block is an *evidence of diastolic overload* of the right ventricle; *in such instances, the conduction defect* is either complete or, more frequently, incomplete, with right axis deviation, and, contrary to the situation in coronary cases, very seldom shows a counterclockwise rotation. The P-wave changes are usually more marked than those *observed in coronary insufficiency*, although of a lesser degree than *those exhibited* by mitrotricuspid patients.

The problem of right bundle branch block, and especially that of a double-peaked R wave in right precordial leads, is of great interest

TABLE 11-2. ETIOLOGY OF BUNDLE BRANCH BLOCK

Type of BBB	*Type of patient*	*Cause of block*
Right	Young	Congenital heart disease Rheumatic heart disease Tricuspid lesions Chagas' disease
	Older	Arteriosclerotic heart disease Cor pulmonale: Acute Chronic
	Exceptional	Toxic factors Infections Tumors Gummas, etc.
Left	With *coronary* insufficiency	Arteriosclerotic heart disease with or without arterial hypertension Calcific aortic stenosis Syphilitic aortic insufficiency
	Exceptional	Tumors Gummas Chagas' disease Myocarditis, etc

in the study of congenital heart disease, having important implications from the standpoint of both electrogenesis and differential diagnosis

In older patients, the appearance of right bundle branch block is usually due to coronary arteriosclerosis. In such instances, the block is usually complete, with left axis deviation and counterclockwise rotation. Lead I usually exhibits a qRs configuration (with a slurred S wave), and lead III shows an rSr′ configuration.

Another common cause of right bundle branch block is *cor pulmonale*, in both its acute and chronic forms. Under these circumstances, AQRS is usually deviated to the right, with clockwise rotation and signs of right atrial enlargement, in addition to other classical signs of these conditions

Bundle branch blocks of any variety may appear in several forms of myocarditis, in thyrotoxicosis, in myocardial disease of unknown etiology, in myocardial tumors, cysts, gummas, trauma, *etc.* In addition, they may be caused by the *toxic effects* of several drugs, such as digitalis, quinidine, and Pronestyl, and also may appear in certain endogenous intoxications, such as hyperpotassemia due to acute or chronic renal insufficiency (Schlesinger and Benchimol, 1956).

CLINICAL FINDINGS

There are no symptoms that are diagnostic of bundle branch blocks, the clinical manifestations that may occur are due either to the etiologic factor involved or to an unrelated clinical syndrome.

There are, however, certain signs which may result from ventricular asynchronism and, therefore, are directly related to the bundle branch block. These signs are (King, 1928) a double cardiac impulse, a muffled and prolonged 1st sound, and a split 2d sound A presystolic gallop rhythm and a midsystolic apical murmur, if present, are not related to the block.

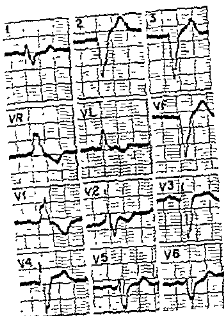
Under special circumstances, the physical signs may suggest the presence of bundle branch block. The most important clinical finding is a distinct and wide splitting of the 2d heart sound (Cossio et al., 1940).

Clinically, *left* bundle branch block may be suggested if there is a presystolic gallop rhythm without heart failure and *a split 2d heart sound with a late aortic component*, so that the reduplication is accentuated by expiration In *right* bundle branch block, there is a *more distinct splitting of the 2d sound with a marked delay in the pulmonic component*, which is highly suggestive Left bundle branch block indicates in most patients a diffuse type of heart disease, whereas right bundle branch block is not necessarily a sign of serious cardiac involvement.

PROGNOSIS

Bundle branch blocks were formerly considered to have an ominous prognostic significance; it is now believed that it is not the conduction disturbance itself but the etiologic factor involved, especially the nature and degree of the myocardial damage, which dictates the prognosis in each case (Schreenivas et al).

Although it is not rare to find bundle branch block as the sole manifestation of cardiac disease (in certain cases with a long survival), these conduction defects usually indicate an extensive myocardial damage, which in most patients is a result of arteriosclerotic heart disease.





A B N - May 1961
masc. 34 years

Fig. 11-36(3). Complete right bundle branch with left axis deviation (-100°). The VCG in the horizontal plane shows a clockwise rotation of the QRS loop with its major portion oriented to the right and anteriorly. Note slight *counterclockwise rotation in the apical portion of the loop. Conduction delay is present in the afferent portion of the loop* The VCG is diagnostic of right *bundle branch block and right ventricular hypertrophy* Note that the initial portion of the *efferent loop is directed leftward and slightly posteriorly, suggesting an associated left ventricular hypertrophy, particularly in the presence of marked left axis deviation.*

TABLE 11-3 BUNDLE BRANCH BLOCK IN CONGENITAL HEART DISEASE

Type of BBB	*Cyanotic*	*Noncyanotic*
Right Ri		with severe pulmonary hypertension
Left axis deviation	AV communis	Ventricular septal defects with mild pulmonary hypertension Ventricular septal defects with or without atrial septal defects
Left	Tricuspid atresia	Coarctation of the aorta Aortic stenosis Patent ductus arteriosus (rarely)

Right bundle branch block is usually considered to have a much less severe prognosis than left bundle branch block. Although this is true in most instances, one must consider each case from the clinical standpoint and not base the prognosis only on the type of bundle branch block.

Several investigators have attempted to determine the average survival time of patients with bundle branch block; some of them have found it to be relatively short. This would seem to indicate an unfavorable prognostic significance of these conduction disturbances. However, more recent statistical studies not only have shown much longer survival periods, but also have pointed out how difficult it would be to estimate how long patients can live with bundle branch block, because it is often impossible to determine the duration of the block prior to its recognition.

TREATMENT

There is no treatment of bundle branch block as such. Therapy must be directed toward the etiologic factors involved, when possible. Although there is no formal contraindication to the administration of *digitalis* in the presence of bundle branch block, if the conduction defect results from toxic effect of the drug, it is imperative to withdraw the medication, at least temporarily. *Quinidine* should be administered most carefully to these patients, under electrocardiographic control; administration should be stopped as soon as there is a further widening of the QRS complex or following the appearance of other types of conduction defect.

INTRAVENTRICULAR BLOCK

Under this designation, a series of intraventricular conduction disturbances has been described, in which the main branches of the bundle of His are not involved. The delay in activation occurs in the more distal segments of the conduction system or in restricted areas of the myocardium in the free ventricular walls. According to Segers, the absence of anatomic lesions of the branches of the bundle of His in certain cases exhibiting electrocardiographic changes which closely resemble those of bundle branch block suggests the possibility of a *focal block* with conduction delay in limited zones of the ventricular myocardium Because certain cases in which the EKG was characteristic of bundle branch block did not reveal, by electrokymographic studies, a delay in the onset of homolateral ventricular ejection, although a prolongation of the ejection period was observed, Segers suggests that the delay in the spread of the activation wave occurs in the lateral walls of the ventricle, representing what he has called *parietal block*. Other authors had previously described cases in which a conduction delay occurred in extensive areas of the ventricular walls at the distal ramifications of the conduction system Oppenheimer and Rothschild described cases with wide QRS complexes and low voltage under the designation of *arborization block*.

According to Grant, parietal block is due to disseminated lesions involving the anterior division of the left branch of the bundle of His; in these cases, the QRS complexes are not necessarily widened, the beginning of ventricular activation is normal, and the conduction delay occurs only in the lateral walls. This results in marked left axis deviation in view of the orientation of the terminal vectors, which are directed leftward and superiorly.

An electrocardiographic pattern showing deep S waves in leads II and III, exceeding the amplitude of the R waves, in the absence of S waves in lead I, has recently been described by Davies and Evans as due to a conduction disturbance in the peripheral branches of the left branch of the bundle of His. They attribute these lesions usually to ischemic changes and believe that the diagnosis of myocardial infarction is highly probable in patients with this type of EKG and with symptoms of cardiac pain.

When the focal lesion is more extensive and is localized in the subendocardial areas of the high anterolateral wall of the left ventricle, in addition to the involvement of the anterior division of the left branch of the bundle of His, resulting in left axis deviation, the initial portions of the QRS complex are also affected, and this has been called *peri-infarction block*, and is characterized by a wide Q wave which is associated with left axis deviation [Fig 11-36(4)].

The main electrocardiographic feature of peri-infarction block is the widening of the angle between the initial and terminal 0.04 sec

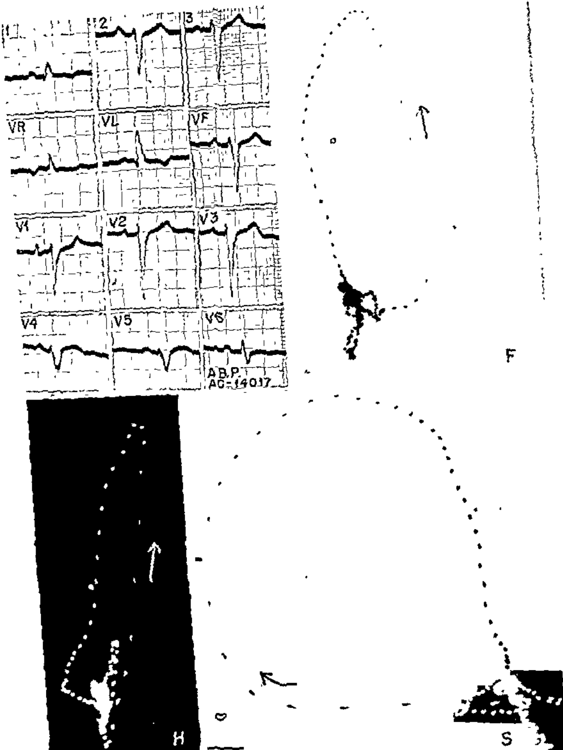


Fig 11-36(4). Focal *peri-infarction block in a 67-year-old male.* The ECG displays wide Q waves in leads I and VL *(high lateral infarction)* associated with left axis deviation *(−85°) and* a QRS *duration of 0.12 sec.* The VCG reveals a counterclockwise rotation *in the horizontal plane,* as well as *a conduction* delay in the terminal portions of the loop *in the three planes*

of the QRS complex. With rare exceptions, in the presence of left axis deviation, when this angle exceeds 100° the EKG is diagnostic of anterolateral peri-infarction block. This type of conduction disturbance was initially described in 1950 by First and coworkers, who interpreted it as being due to the involvement of extensive areas of the subendocardial portions of the ventricles and of the Purkinje network. Under these circumstances, the impulse spreads through the noninvolved myocardium around the infarcted area, and its conduction is delayed at this point.

Finally, a type of *diffuse intraventricular block* has been described that resembles left bundle branch block, with Q waves in left precordial leads.

These cases are apparently due to a diffuse conduction disturbance through the ventricular wall, resulting from left ventricular hypertrophy, diffuse myocardial fibrosis, quinidine toxicity, or hyperpotassemia.

GRAPHIC DATA IN BUNDLE BRANCH BLOCK

PHONOCARDIOGRAM

The 1st sound is *prolonged* and lasts more than 0.16 sec. It is frequently of low amplitude. *Splitting of this sound* has been described by several authors. However, this observation is not confirmed by "stethoscopic" tracings and should be attributed to either inadequate or different techniques. Ventricular asynchronism results in the delay of the contraction of one ventricle over that of the other of about 0.04 to 0.05 sec. This interval is too short for causing a splitting of the central phase of the 1st sound, which lasts from 0.06 to 0.08 sec. However, it causes prolongation of the sound in both right and left bundle branch block. If *left* ventricular hypertrophy and intraventricular block add their effects to that of *left* bundle branch block, the delay between the contractions of the two ventricles may reach 0.06 sec or more. Then, closing of the mitral valve (first valvular event of the left heart) takes place at the time of opening of the pulmonic valve (second valvular event of the right heart) because the normal isometric tension period (about 0.05 sec) lasts as long as the pathologic interval between the contractions of the two ventricles. The phonocardiogram then reveals *three groups of vibrations*. the first is due to tricuspid closure; the second,

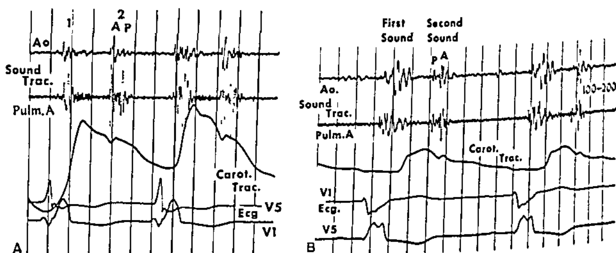


Fig. 11-37. A. Simultaneous phonocardiograms over the aortic (Ao) and pulmonic (Pulm. A.) areas, compared with carotid tracing and unipolar ECG chest leads. Time, 0.1 sec. The second component of the 2d sound is visible only in the pulmonic tracing and does not coincide with the incisura of the carotid pulse. Diagnosis: *right ventricular delay due to right bundle branch block*. M. Simultaneous phonocardiograms over the aortic (Ao) and pulmonic (Pulm. A.) areas, compared with carotid tracing and unipolar ECG chest leads. Time, 0.1 sec. The second component of the 2d sound is visible over both areas of the base and coincides with the incisura of the carotid pulse. The aortic 1st sound occurs later than the pulmonic 1st sound. Diagnosis: *left ventricular delay due to left bundle branch block*.

to pulmonic opening plus mitral closure; the third, to aortic opening. A *similar phenomenon*, with delay of right ventricular events, occurs when *right intraventricular block* and *right ventricular hypertrophy* add their effects to that of *right bundle branch block*.

It is probable that a new study by means of "*selective phonocardiography*," with its scanning of adjacent bands of sounds, will reveal different data, possibly including a "splitting" of the 1st sound. (The quotes are necessary because the 1st sound already presents a "physiologic" splitting when recorded in normal subjects in the band 240 to 460 cps.)

The 2d sound, being shorter, is constantly split in bundle branch block. In the case of *right bundle branch block*, as the pulmonic component *normally follows the aortic component of the 2d sound by* 0.02 *sec*, the 2d sound is widely split, and there is an interval of about 0.05 to 0.07 sec between the aortic and the subsequent pulmonic component (Fig. 11-37A). In the case of left bundle branch *block*, the opposite occurs. If there is only a slight delay of the aortic component, it will fall at the time of the pulmonic component (*no splitting of the 2d sound*). If, on the other hand, there is a severe delay, then the aortic component will *follow* the pulmonic component *by 0.02 to 0.04 (paradoxical splitting of the 2d sound, Leatham)* (Fig. 11-37B).

CAROTID TRACING, JUGULAR TRACING

The delay between the beginning of the 1st sound and the rise of the carotid pulse (usually about 0.05 sec) *is increased* and lasts from 0.07 to 0.08 sec in *left bundle branch block*. The incisura of the carotid pulse *coincides* in normal subjects with the main vibration of the *2d sound* (aortic component). In *left bundle branch block*, it coincides with *the 2d phase* of the split 2d sound (*aortic component*) (Fig. 11-37B). The rise of the carotid pulse has a normal relationship to the beginning of the 1st sound in *right bundle branch blocks*. The incisura has a normal relationship to the 1st phase of the split 2d sound (aortic component) in this type of block (Fig. 11-37A) *while the* pulmonic component occurs later.

In *right bundle branch block*, the study of the jugular tracing is of importance. *the peak of the V wave is markedly delayed* and occurs 0.08 to 0.14 sec after the end of the 2d sound (or after the 2d phase of the 2d sound, if this is split). In other words, the V wave, which usually occurs 0.08 to 0.14 sec after the 2d sound, has the same relationship to the pulmonic component (2d phase) of *this* sound, when it is split.

ELECTROKYMOGRAM

This method may be applied to the study of pulmonic or aortic pulsations. *In most cases*, it may be *applied to the study* not only of left ventricular but also of right ventricular contraction. Moreover, right atrial tracing is so deeply influenced by right ventricular contraction that the phases of right ventricular dynamics may be studied even by recording a right atrial border tracing. The best technique is that of recording simultaneously a *high left ventricular tracing* and a pulmonic tracing, then, a right ventricular (or right atrial) tracing with an aortic tracing.[2] The study may be completed by the simultaneous observation of the anterior (right ventricle) and posterior (left ventricle) surfaces of the heart. It should be kept in mind that while direct comparison of the two ventricles has a decisive importance, *comparison of one ventricle with one pulse (or of the aortic and pulmonic pulses)* is less significant on account of possible interaction of peripheral factors which may accelerate or delay the valvular events.

Normal time *relationships between the two* ventricles and the two large vessels were studied by the author and his coworkers (1948) and by Samet and coworkers (1950b). In spite of slight individual and phasic variations, it can be assumed that the two ventricles and the two large arteries present pulsations which succeed each other within 0.02 sec. The most *common* is the precession of the pulmonic pulse by 0.020 sec (Part 4, Chap. 8).

In about 30 per cent of the cases of *left bundle branch block*, left ventricular contraction and the aortic pulse are delayed over the

[2] If one has *only a pickup unit*, the study should be made in the following way: (1) aortic electrokymogram (EKy) plus sound tracings, (2) pul- ... of the carotid tracing *as timer is confusing* in these cases of bundle branch block because the carotid pulse is necessarily delayed in left bundle branch block.

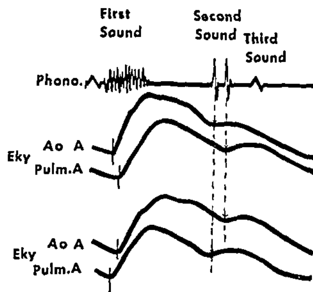


Fig. 11-38. Scheme of the electrokymograms of the aortic and pulmonary arches in right (above) and left (below) bundle branch blocks with ventricular asynchronism. (*From Luisada. Heart Beat Hoeber, 1953.*)

right ventricular and the pulmonic pulse by about 0.03 to 0.05 sec (Fig 11-38). If there is hypertrophy or intraventricular block of the left side, the delay is greater. Hypertension of the greater circulation increases the delay revealed by the rise of the pulse, decreases that revealed by the incisura.

In about 30 per cent of the cases of *right bundle branch block*, the right ventricular contraction and the pulmonic pulse are delayed over the left ventricular and the aortic pulse by about 0.03 to 0 05 sec (Fig. 11-38). If there is hypertrophy of the right ventricle or intraventricular block of the right side, the delay is greater. Hypertension of the lesser circulation increases the delay revealed by the rise of the pulse, decreases that revealed by the incisura. Systemic hypertension may partly neutralize the effect of right bundle branch block, so that the delay is less apparent.

In both types of block, a prolongation of the phase of isometric relaxation was observed A large percentage of cases of bundle branch block, whatever the side, seem to present a bilateral delay of contraction upon EKy studies Phonocardiographic studies reveal a much larger percentage of asynchronism than EKy studies.

CONDUCTION

[illegible]

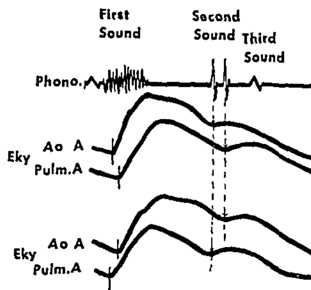


Fig. 11-38. Scheme of the electrokymograms of the aortic and pulmonary arches in right (above) and left (below) bundle branch blocks with ventricular asynchronism. (*From Luisada. Heart Beat. Hoeber, 1953.*)

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In about 30 per cent of the cases of *right bundle branch block,* the right ventricular contraction and the pulmonic pulse are delayed over the left ventricular and the aortic pulse by about 0.03 to 0.05 sec (Fig. 11-38). If there is hypertrophy of the right ventricle or intraventricular block of the right side, the delay is greater. Hypertension of the lesser circulation increases the delay revealed by the rise of the pulse, decreases that revealed by the incisura. Systemic hypertension may partly neutralize the effect of right bundle branch block, so that the delay is less apparent.

In both types of block, a prolongation of the phase of isometric relaxation was observed. A large percentage of cases of bundle branch block, whatever the side, seem to present a bilateral delay of contraction upon EKy studies. Phonocardiographic studies reveal a much larger percentage of asynchronism than EKy studies.

11

The Wolff-Parkinson-White syndrome and other forms of preexcitation

EUGENE LEPESCHKIN

L. Wolff, J. Parkinson, and P. D. White described (1930) a syndrome which usually appeared in young persons with occasional paroxysmal tachycardia (but otherwise normal hearts) and was characterized by *a short P-R interval and a wide QRS complex* resembling bundle branch block. Many of these persons showed on other occasions normal QRS complexes with normal P-R intervals, the P-J interval to the S-T junction usually remaining the same length as in the aberrant complexes. Öhnell, who studied the syndrome extensively (1940), showed that it was caused by *premature excitation* of a part of the ventricle by the atrium, and introduced the term *preexcitation* to designate this as well as other less characteristic electrocardiographic patterns. In the typical pattern, the wide premature component of the QRS complex is of relatively low voltage and shows a distinct kink with the slender terminal portion of the QRS complex, which corresponds to normal activation of the ventricles through the AV node and is nearly identical in the normal and the aberrant complexes. In the vectorcardiogram, this premature portion usually moves two to three times more slowly than the rest of the QRS loop (Grishman and Jaffe, Wolff and Richman). The slow premature portion has been called by Segers et al. (1947) *the delta wave*, as it resembles the Greek letter Δ in configuration (Figs. 11-39, 11-40).

In some cases, not only the initial, premature portion of the QRS complex but also its terminal portion is wide and slurred, and the form of the QRS complex is identical with that of bundle branch block. This pattern appears when normal activation through the AV node is delayed or absent, and the ventricles are activated exclusively in the premature manner, directly from the atrium. In such cases, the P-R interval of the normally conducted complexes is usually prolonged (Blom) or the AV bundle is completely interrupted (Mahaim, Scherf et al.). This pattern was designated as *type F* by Öhnell, but in order to avoid confusion with the grouping according to the direction of the delta wave, it will here be called *complete preexcitation*. In other cases, the premature component of the QRS complex is of very short duration and may be hard to distinguish from a normal slurred onset of the R wave, the duration of the QRS complex in these cases is accordingly not prolonged beyond the upper normal limits (Fig. 11-41). This pattern results when the normal conduction through the AV node is especially rapid, and only a small section of the ventricles can be excited directly from the atria before the rest of the ventricular mass is excited through the normal conducting system. It is usually seen in persons with normally short P-R intervals, such as children or young women. Relatives of persons with this pattern also tend to show a short P-R interval (Koch). This pattern has been designated as *type A* by Öhnell but will be called here *rudimentary preexcitation*, to avoid confusion. A third atypical pattern, designated as *type E* by Öhnell, shows the usual slurred configuration of the QRS complex but *a long or normal P-R interval*, and is due to a delay in both the normal and the premature excitation of the ventricle, the P-R interval of the normally conducted beats is always prolonged (Mahaim, Koch,

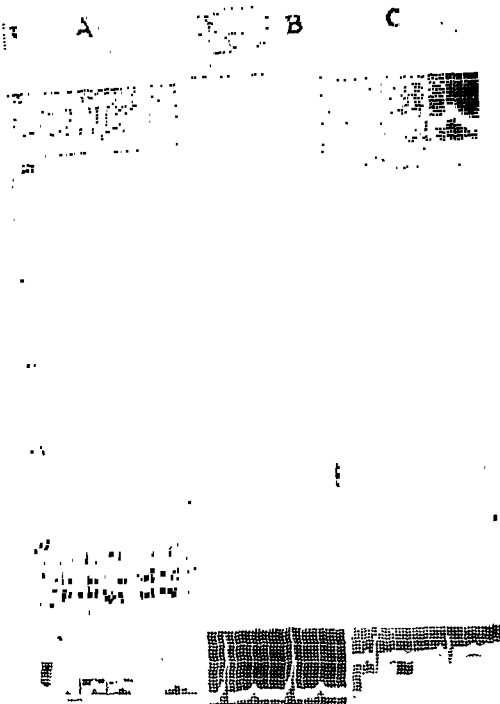


Fig 11-39 A Electrocardiogram of a 12-year-old girl *during* an attack of paroxysmal tachycardia *The P* waves follow the QRS complex and *are diphasic, but* mainly upright in leads I to III The QRS complexes are narrow, the *alternation in* amplitude of the R wave *is common* in *all* supraventricular tachycardias with *very high* ventricular rates. B. After termination of the attack, sinus rhythm *with type B* preexcitation is present. C After *medication* with quinidine, preexcitation *disappears The fusion of the T wave with the U wave is part of the* quinidine *effect.*

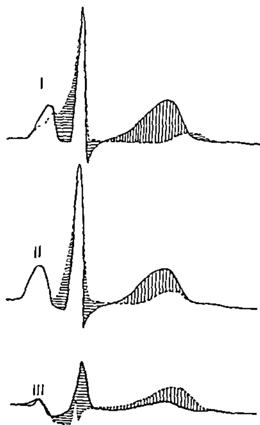


Fig. 11-40. The limb lead electrocardiograms of Fig. 11-39B are superimposed on corresponding leads of the same patient taken several weeks later when no preexcitation or quinidine effects were present. It can be seen that the increase in the positive area of the QRS complex (horizontal shading) is equal to the decrease in the positive area of the T wave and S-T segment (vertical shading).

Glushien and Goldblum, Pick and Katz). This pattern will be called *delayed preexcitation*.

According to the direction of the premature component of the QRS complex in the precordial leads, Rosenbaum, Hecht, Wilson, and Johnston distinguished two groups of cases. In "group B" this component is upright in the unipolar precordial leads V_3 through V_6 but inverted in V_1 (and sometimes also in V_2), the right, lower, and posterior portions of the thorax, and usually also aVF; in the frontal plane, this component shows usually left axis deviation but sometimes a normal axis. In this group, the highest negative voltage of this component was found in leads from the right atrium near the tricuspid valve and in the lower esophagus, while leads from the cavity of the right ventricle and the coronary vein showed a positive premature component (Grishman et al., Giraud et al.; Hecht et al., 1957). This indicates that the prematurely excited ventricular muscle is *on the posterolateral epicardial surface of the right ventricle, near the AV groove*. In group A, the premature component of the QRS complex is negative on the back but positive in leads V_1 through V_6 and usually also in aVF, so that its axis in the frontal plane is usually normal or deviated to the right, and only occasionally deviated to the left. In intracardiac leads, some cases of this group showed the same findings as in group B, and the difference in the configuration of leads V_1 to V_2 in these cases was therefore attributed to a different position of the heart (Grishman et al.). However, in cases of this group

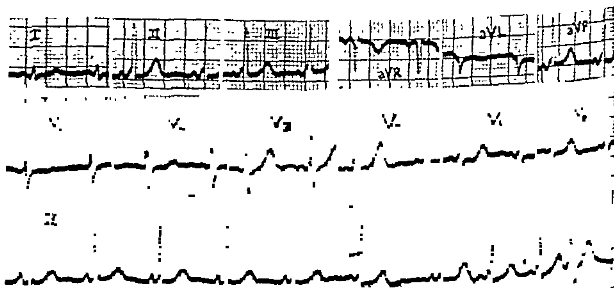


Fig. 11-41. Electrocardiogram of a 22-year-old woman with rudimentary preexcitation of type A, who complained of occasional rapid heart action. No electrocardiogram could be taken during the attack. The lower strip shows "concertina effect," leading to pseudonormalization during the pressor phase of the Valsalva maneuver and to increased preexcitation during the postpressor phase. One ventricular extrasystole appears at the end of the tracing.

which showed an *isoelectric* or negative premature *component* in leads I and V_6, this component was positive in the right atrium and ventricle, but *deeply negative* in the coronary vein, which is in contact with the posterior *aspect of the left ventricle near the AV groove* (Giraud et al.). It was, therefore, concluded that *this is the site of the prematurely activated portion of the ventricle*. Such cases constitute *less than 20 per cent* of all *persons* with the Wolff-Parkinson-White syndrome. In both groups, the subepicardial location of the prematurely excited section accounts for the low voltage and long duration of the premature component of the QRS complex, since the rapidly conducting Purkinje fibers do not penetrate to the epicardium

Holzmann and Scherf and, independently, Wood and coworkers suggested that the premature excitation of the ventricle by the atria could take place through an *accessory* bundle similar to that first described by Kent (1893) This bundle consists of nonspecialized muscle and can, therefore, be expected to conduct excitation *more rapidly* than the specialized thin muscle fibers of the AV node, whose function is to delay excitation of the ventricle. A subepicardial accessory muscle bundle connecting the posterolateral aspects of the right ventricle and atrium was actually found in two cases with the preexcitation syndrome (Levine and Burge, Lev et al), and three similar subendocardial bundles were found in another case (Wood et al.), in still another case, the connection was between the atrial and ventricular septa on the right side (Segers et al, 1947) All these cases belonged to group B A subepicardial connection between the *left atrium and ventricle* was found in two cases (Öhnell, Mahaim), and an additional case showed both a right-sided and a *left-sided connection* (Kimball and Burch) All these *cases belonged* to group A and showed a negative premature component in lead I; the electrocardiographic pattern accordingly is in keeping with the anatomic location of the aberrant pathway On the other hand, the incidence of this pathway in routine autopsies is no greater than that of preexcitation (Lev et al.)

However, in several persons who had shown preexcitation, *no* accessory bundle could be found despite careful histologic study (Soderstrom, Hecht et al, 1957) In these cases, another explanation must be sought Holzmann and Scherf suggested that preexcitation can be due to stimulation of an acquired irritable ventricular center by the stretching effect of atrial contraction; such a center could also be set off by the action potential of atrial fibers (Segers et al, 1947) As these effects would be great*est near the AV* border, especially if there is intimate contact between atrial and ventricular muscle fibers, as in the cases of Söderström and Langendorf et al., the localization of the premature component would be in keeping also with this hypothesis Stable preexcitation complexes were often seen to appear during cardiac catheterization, Giraud et al. found this in more than one-third of all catheterizations Prinzmetal et al (1952) could elicit such complexes most commonly by applying pressure, or a subthreshold electric current, to the inner surface of the ventricles through the atrium. In these cases, atrial contraction was probably transmitted mechanically through the catheter or the stimulating electrode. Preexcitation also could be elicited by injection of aconitine or epinephrine into the ventricular septum near the *AV* border (Frau and Maggi), and may also appear after intravenous injection of strophanthin (Vakil) or epinephrine (Fig 11-42) All these procedures increase ventricular excitability In all these cases, the complexes with short P-R interval and wide QRS complex usually showed transitions to ventricular parasystolic rhythms or coupled extrasystoles showing no relation to the P waves It is very difficult to decide in *a given* case whether true coupling of *the ventricular* complexes to the P *waves exists or whether* the relation between the wide QRS complex and the P wave is a fortuitous one Furthermore, there are many factors which may cause synchronization of P waves to the preceding QRS complexes (Rosenbaum and Lepeschkin), and the designation of *preexcitation* cannot be applied to *them True preexcitation* becomes probable *if the short P-R* interval remains *completely constant* during a series of beats *(Pick and Katz)*, but it can be proved definitely *only if this interval* remains con*stant even* in the presence of spontaneous or *induced variations* of the P-wave rhythm A *mechanical* coupling can be expected to pro*duce a rather* loose synchronization, since the *instant* when a given tension is exerted on the *ventricle* would vary with the stroke volume,

heart position, etc. An electrical coupling, on the other hand, would be much more constant, since the shape of the P waves and the sequence of activation of atrial muscle near the AV border show only insignificant variations.

A third hypothesis, advanced by Prinzmetal and coworkers (1952), is that the premature activation of the ventricle is due to accelerated conduction in part of the fibers of the AV node. Experiments considered as proof of this hypothesis are open to criticism (Sodi Pallares, 1956, Hecht et al., 1957). Furthermore, it would not explain the slow ascent of the premature component of the QRS complex, since premature activation of the rapidly conducting specific system would cause a rapid initial component

The incidence of the typical Wolff-Parkinson-White pattern is 0 02 to 0.04 per cent in children (Landtman; Vacheron), 0.07 to 0.1 per cent in apparently normal adults and in ambulatory patients (Hecht et al., 1957), and 0 16 per cent in hospitalized patients. This increased incidence with age and severity of disease, together with its appearance in infections or rheumatic heart disease, could be considered as favoring an acquired genesis of the syndrome The explanation of Pick and Katz, that any acquired factors which impair normal AV conduction would facilitate congenital aberrant conduction, does not seem plausible, since aberrant conduction takes place before normal conduction However, since conduction in aberrant anatomic pathways may be present only occasionally (Lyle), the increased incidence of aberrant complexes under abnormal conditions may be simply the result of the electrocardiograms being taken more often and in longer strips. On the other hand, the smaller incidence in children may be due to the short normal P-R interval, which may mask all or part of the aberrant conduction.

The fact that preexcitation was repeatedly found in two or more members of the same family (Öhnell; Koch; Hecht et al, 1957) is strongly in favor of a congenital origin of this anomaly, as are the occurrence of other congenital anomalies and the high incidence (0 7 per cent) of preexcitation in persons with congenital heart disease (Hecht et al, 1957) and the fact that preexcitation is twice as common in males as in females in all age groups (Vacheron; Lown et al.).

Increase of the heart rate, whether spontaneous or due to exercise, the Valsalva maneuver (Fig. 11-41), standing up, fever, atropine, amyl nitrite, or Banthine, usually causes the premature component of the QRS complex to become shorter and the QRS complex more normal, this is because of acceleration of normal AV conduction, which causes more of the ventricle to be activated in a normal manner. Occasionally, the premature component may disappear completely, this "pseudonormalization" can be distinguished from true normalization by the fact that the P-R interval remains short True normalization may occur also, in this case the P-R interval becomes longer. This can be explained by assuming either that

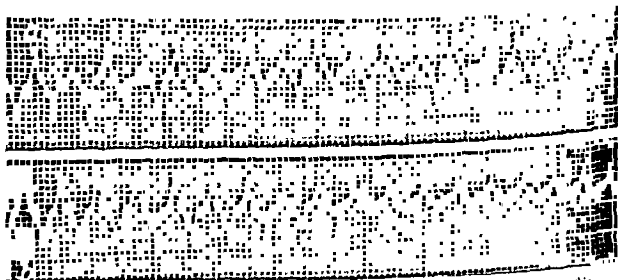


Fig. 11-42. Alternating preexcitation appearing in a cat after injection of myocardial sympathin. B The premature component of the QRS complex appears progressively later and disappears at the end of the tracing

at high heart rates conduction in an anatomic aberrant pathway does not take place because of fatigue, or that the mechanical effect of atrial contraction is smaller because of the decreased stroke volume On the other hand, decrease of heart rate, such as that caused by carotid sinus pressure, the late phase of the Valsalva maneuver (Fig 11-41), or medication with *Prostigmine*, *Mecholyl*, or *digitalis*, usually increases the duration and magnitude of the premature component of the QRS complex because of slowing of normal AV conduction During this effect, the P-R interval remains short but the P-J interval increases In many cases, the above factors led to the appearance of preexcitation complexes

The remarkable constancy of the P-R interval in preexcitation may be due to the fact that an aberrant pathway, consisting of nondifferentiated ventricular muscle, would not be influenced by the vagal effects which cause prolongation of the normal AV conduction together with bradycardia It would also be in keeping with an electrical, but not with a mechanical, excitation of a ventricular irritable focus by the atrium, as mentioned above The only factors which influence the P-R interval seem to be *quinidine* and *procaine amide*, which usually cause the premature component of the QRS complex to appear progressively later, to become smaller, and finally to disappear completely (Blinder et al , Zapata Dias et al) In these cases, the P-R interval becomes longer while the P-J interval is usually unchanged In some cases, normalization takes place abruptly The action of these drugs would be in keeping with a slowing of conduction in an accessory bundle, but not in the AV node, since they have a greater effect on nonspecific ventricular muscle It would also be in keeping with an ectopic ventricular focus stimulated by atrial activity, as the same drugs decrease ventricular excitability, a gradual and considerable prolongation of the P-R interval would be more difficult to explain on this basis, since the moment of excitation would then occur considerably after the maximal electrical and mechanical effects of atrial excitation The occurrence of delayed preexcitation would also be difficult to explain on this basis Finally, the occurrence in some cases of preexcitation of Wenckebach's periods, i e , of progressive prolongation of the P-R interval leading to complete AV block followed by shortening of the P-R interval (Levine and Burge, Scherf et al., 1953; Hecht et al., 1957), could not be explained on any other basis except that of an aberrant AV bundle.

When AV nodal beats occur in preexcitation, either spontaneously or during the initial, bradycardiac action of atropine, during carotid sinus pressure, or after injection of Neosynephrine (Ohnell), they always show a normal QRS complex if the P wave follows the QRS complex. In these cases, the ventricle is excited entirely through normal pathways before preexcitation can take place Occasionally, when the P wave precedes the QRS complex slightly, a delta wave may appear, but it is always shorter than in the usual preexcitation complexes In a few cases, this wave was present even when no P wave preceded the QRS complex; in these cases the rhythm could have originated in the accessory bundle, or this bundle could have originated in the AV node itself

Paroxysmal tachycardia was found in about 70 per cent of all cases showing the Wolff-Parkinson-White pattern, in children, this percentage was 93 per cent (Vacheron). On the other hand, it constitutes about 5 per cent of the cases of paroxysmal tachycardia, in children this percentage was 12 per cent (Nadas et al) The higher incidence in children can be explained by the fact that electrocardiograms in children are seldom taken unless there is a conspicuous alteration of rate or an arrhythmia In most cases the QRS complexes were regular and narrow, and were followed after about 0.10 sec by inverted or diphasic P waves, the premature portion of the QRS complex was absent. The tachycardia was therefore designated as nodal, but, in contrast to typical nodal tachycardia, the P waves were often upright in lead I The appearance of this type of tachycardia can be explained by means of a special form of "circus movement" from the ventricle to the atrium through an accessory AV bundle, and back to the ventricle through the normal AV conduction system. It could not be explained at all on the basis of an excitable ventricular center, for this would cause a ventricular tachycardia.

The beginning and end of the paroxysmal tachycardia was studied repeatedly only in a few cases. In two of them (Juncadella Ferrer,

Tommaselli), frequent atrial extrasystoles were present; if they appeared late, they were followed by QRS complexes with delta waves, but if they appeared early enough, they were followed by a narrow QRS complex, followed in turn by a diphasic P wave and an access of paroxysmal tachycardia. Still earlier extrasystoles were followed by narrow QRS complexes only, or were blocked. Apparently circus movement becomes possible only if an atrial extrasystole appears early enough to find the accessory bundle still refractory but late enough for it to recover by the time excitation is conducted to the ventricle The attack was terminated either by a diphasic P wave after progressive lengthening of the P-R interval (block in the AV node) or suddenly by a QRS complex (block in the accessory bundle). In other cases (Rosenbaum et al., 1945; Katz and Pick), the attacks were initiated in the same way by lower nodal extrasystoles, with the first few complexes of the tachycardia showing a wide QRS complex without a slow initial component, because of aberrant intraventricular conduction. In the case of Lyle, the atrial extrasystoles elicited runs of tachycardia with wide QRS complexes showing delta waves, in this case, the normal conducting system could have been still refractory while excitation was conducted down the accessory bundle, but became conducting by the time excitation reached it retrogradely from the ventricle These cases show that a premature stimulus is necessary to establish circus movement and explain the numerous observations in which no paroxysmal tachycardia appeared until the occurrence of some acute infection, which could have precipitated extrasystoles responsible for circus movement In most cases the tachycardia can be interrupted by digitalis, while in some, quinidine is more effective This can be explained by assuming that circus movement can be terminated either by blocking the AV node with digitalis or by blocking the accessory bundle with quinidine

In a minority of the cases with preexcitation, *atrial fibrillation* is registered during the accesses of paroxysmal tachycardia, and a few cases show *atrial flutter* (Pick and Katz). The case of Tommaselli shows clearly how the typical "nodal" type of tachycardia attributed to circus movement through the aberrant bundle can be transformed into atrial flutter and finally into atrial fibrillation; any rapid stimulation of the atria can lead to the same sequence. These arrhythmias can accordingly be explained on the basis of an accessory bundle, but not on that of an excitable ventricular center. When atrial fibrillation is present, runs of normal QRS complexes usually alternate with groups of complexes showing very wide delta waves (complete preexcitation). These groups can be explained by assuming that when excitation takes place over the accessory bundle, the normal AV bundle is excited later and retrogradely, and therefore recovers its conductivity later than the accessory bundle, so that the constantly circulating fibrillation waves are likely to enter the accessory bundle again (Pick and Katz). As in atrial fibrillation, coordinated atrial contractions are absent, the appearance of preexcitation in these cases cannot be explained by mechanical effects of atrial contraction, while stimulation by electrical effects would still be possible. One peculiarity of atrial fibrillation with preexcitation is that the ventricular rate is usually very rapid, and the usual slowing effect of digitalis medication on this rate is absent (Katz and Pick, Giraud et al.). This can be explained by the fact that this slowing effect is due to a blocking effect of digitalis on the AV node, the drug would not have effect on a muscular accessory pathway. *Quinidine*, which blocks also the accessory pathway, must be combined with digitalis in such cases.

In many cases of preexcitation, the paroxysmal tachycardia was interpreted as being of ventricular origin, but closer scrutiny of the tracings always made it seem probable that in reality *atrial fibrillation with complete preexcitation* was present (Langendorf et al; Giraud et al.) True ventricular tachycardia becomes probable only in cases where ventricular extrasystoles of the same form had appeared previously (Frau and Maggi). In these cases, the explanation of the syndrome as due to an excitable ventricular center is more likely.

Occasionally the slope of the premature component of the QRS complex in preexcitation complexes may be so slight that this component can be mistaken for an ascending P-R segment; if this slope is less than 2.5 mv/sec, the term "type B" was used by Öhnell, but we shall call this pattern *low-voltage preexcitation*. This type often results from superposition of a descending P-R segment

n the *delta wave* and usually becomes more pical with slowing of the heart rate, especially n the precordial leads. A much more common attern shows a short P-R interval but an apparently normal QRS complex. It can represent *preexcitation* with a very steep and rapid delta wave, but this diagnosis can be made with certainty only if QRS complexes of different configuration and with a longer P-R interval can be observed to appear. In this type of "rapid preexcitation," designated as "type C" by Ohnell, the accessory bundle could terminate in the bundle of His. On the other hand, the pattern can correspond to accelerated conduction in the AV node. Lown et al found that the incidence of *paroxysmal* tachycardia in such cases was much less than in typical preexcitation (only 10 per cent), while the percentage of cases among females was much greater (70 per cent), most of them had signs of adrenal cortical overactivity. In some of these cases, the P-R interval became longer after digitalis administration but the QRS complex remained identical, and in these an accessory bundle could be definitely excluded.

The recognition of preexcitation is important, first of all because, although deaths due to paroxysmal tachycardia have been reported in this condition, its prognosis is much better *than* that of left bundle branch block with *which it may* be confused. The differentiation is easy in the presence of a typical delta wave, but complete preexcitation may look almost exactly like bundle branch block, especially if the P-R interval *is borderline* or atrial fibrillation is present. Usually, the initial *slope of the* QRS complex in right precordial leads is steeper in *bundle branch* block than in preexcitation, but sometimes *a definite* diagnosis can be made only by conversion *to sinus rhythm or* by application of agents which cause acceleration of AV conduction or true normalization. A Valsalva maneuver *or* subcutaneous injection of 1 mg atropine may cause the appearance of nodal escape beats with a normal QRS complex, accelerated AV conduction, or pseudo normalization. Slow *intravenous* injection *of procaine amide* at the rate of 200 mg/min up to 1 Gm caused normalization in 7 out of 9 cases without side *effects* (Zapata Dias et al.)

Preexcitation *complexes* showing a *negative* delta wave in leads I or II *or* III *may* imitate the deep Q wave of myocardial *infarction. On* the other hand, *positive* delta waves may prevent the deep Q waves of *infarction from* appearing, and old *infarction* can be recognized *in such* cases only after normalization. The changes of the R wave and S-T segment caused by infarction can also be masked by preexcitation, but in most cases, *closer inspection allows their recognition*. The *secondary* changes of the T wave and S-T segment in [illegible]tation are always opposite in direction [illegible] ponent (Fig 11-40). The total QRS [illegible] (ventricular gradient) remains the same (Bercun et al.). Accordingly, if the S-T segment [illegible] in a lead where the premature [illegible] tive or only slightly positive, these changes [illegible] to be primary and to indicate additional myocardial *damage. It must* be emphasized, however, that the primary T-wave *inversion* may appear in preexcitation without myocardial infarction after accesses of paroxysmal *tachycardia*, especially if treated with quinidine, in these cases, the T-wave *changes* remain after normalization. Another source of error may appear in rudimentary preexcitation, where the change in the QRS area may not be sufficient to cause an abnormal configuration of the QRS complex *but sufficient* to cause depression of the S-T segment and a *diphasic T wave*, which can be erroneously interpreted as *denoting myocardial* damage.

In the presence of *paroxysmal tachycardia*, the recognition of preexcitation is important *for treatment, since* if circus movement through the *accessory* bundle is the cause of tachycardia, quinidine *or procaine* amide *should* be beneficial even if this appears to be *"supraventricular"* Quinidine will also *prevent* the appearance of single atrial extrasystoles, which are often *instrumental in precipitating an attack*. Recently *Chlorpromazine* has been found beneficial, alone or in conjunction with *procaine amide, even where* the latter alone was ineffectual (Giraud *et al.*). The presence *of upright P* waves in lead I *in "nodal tachycardia"* or of the peculiar groups of wide QRS complexes in atrial fibrillation makes preexcitation *probable*, but it can *be established* only when delta waves can be *identified in* previous tracings or *appear* between attacks. It must be *emphasized* that *after* the tachycardia has

been stopped with quinidine, preexcitation complexes may not appear as long as the quinidine effect persists; an electrocardiogram repeated several days after termination of treatment is therefore more likely to disclose preexcitation (Blinder et al.). The ultimate goal in the treatment of tachycardia due to preexcitation would be to remove surgically the accessory bundle or the point of intimate contact between atrial and ventricular muscle. Its precise localization can be made satisfactorily from the configuration of the delta wave.

11

Double rhythms (pararrhythmias)

CORNELIO PAPP

One of the basic laws of cardiac physiology is that "a pacemaker working at a faster rate suppresses any potential secondary or tertiary pacemaker having a lower rate." Since, under normal conditions, the SA node forms impulses at a faster rate than the AV node or the intraventricular centers, in normal conditions it remains in sole control of cardiac rhythm.

In *double rhythms,* two pacemakers are active simultaneously, one of which is usually the SA node. The secondary pacemaker, which *may be situated anywhere in the atria,* the node, the bundle, or its branches, may form impulses at a higher or lower rate than the SA node For the existence of a double rhythm, it is essential that the slower pacemaker be protected from the faster one Such a "protection block" has been shown to exist and prevents the *suppression of the rhythm* created by the SA node or the ectopic pacemaker, whichever is the slower of the two

Double rhythm may manifest itself in two different forms

1 *AV dissociation* Here the rhythm of the atria is directed by the SA node, that of the ventricles, by the AV node. The SA rhythm, usually slower, is protected by a unidirectional block which prevents the nodal impulse from spreading backwards to the SA node, while *there is no obstacle to the spreading of sinus impulses to the AV node* The conducted SA impulses produce a transient disturbance of the AV nodal rhythm (dissociation with interference)

2 *Parasystole* The SA node is in command of atria and ventricles An ectopic (usually ventricular) pacemaker working at a slower rate, is protected by a *block of entry* from the faster SA impulses. This block, too, is unidirectional and *allows the ectopic pacemaker to assert itself and to interfere with the basic rhythm.*

The main difference between these two double rhythms—apart from the dissociated activity of the two pairs of chambers in AV dissociation—consists in the way the two pacemakers interfere with each other. In AV dissociation, it is the SA node which disturbs the ectopic pacemaker, while *in parasystole, it is* the ectopic pacemaker which interferes with the SA rhythm.

ATRIOVENTRICULAR DISSOCIATION

When the rate at which impulses form in the AV node is superior to the rate at which it *receives impulses from the SA node, AV nodal rhythm results. This condition arises* when impulse formation is depressed in the SA node or exalted in the AV node, or when both these conditions exist. Since the physiologic property of the nodal tissue is that of unidirectional conduction, and impulses are *transmitted readily* from atrium to ventricle (but only with *difficulty in the reverse direction*), *retrograde block may arise and the SA* node will continue to beat independently *How* many of the SA impulses are *so timed as to* fall outside the refractory period and "capture" the ventricle depends upon the relative *rates of the two pacemakers and the duration of the refractory period of* both the junctional tissues and the *ventricles. If the AV* nodal rhythm is rapid, the refractory *period* shortens, and, with a slow SA rhythm, ventricular

been stopped with quinidine, preexcitation complexes may not appear as long as the quinidine effect persists; an electrocardiogram repeated several days after termination of treatment is therefore more likely to disclose preexcitation (Blinder et al.). The ultimate goal in the treatment of tachycardia due to preexcitation would be to remove surgically the accessory bundle or the point of intimate contact between atrial and ventricular muscle. Its *precise localization can be made satisfactorily* from the configuration of the delta wave.

Since in most of the published cases, the ventricular rate was faster than the atrial rate, this was thought to be an essential feature of AV dissociation Laubry and Lequime (1933) and Laubry and Puddu (1936) proved that this is not necessarily so and that certain factors (digitalis, toxic agents), which may produce SA depression and a passive escape of the node, may also exalt nodal activity They published cases with ventricular rates faster than or similar to the SA rates (*isorhythmic dissociation*).

The QRS complexes are commonly supraventricular. They may have a bizarre shape, because of aberrant intraventricular conduction caused by early appearance (Fig. 11-44B) of an infranodal pacemaker.

The QRS complexes conducted from the SA node may have a slightly different shape (Fig

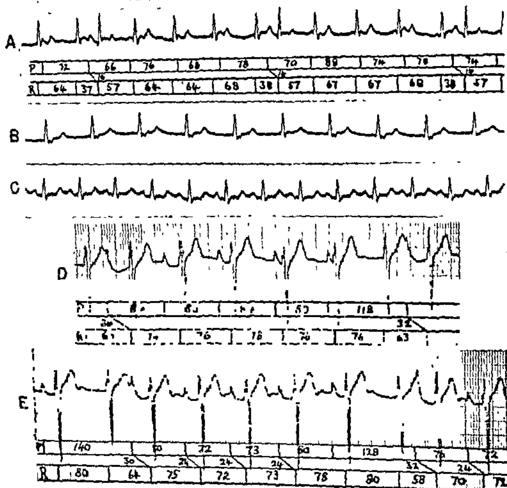


Fig. 11-43 Lead II A. *Mar. 27, 1957* AV dissociation with *interference*; third, eighth, and last beats, which are premature, are conducted. B. *Mar. 29* nodal rhythm with *retrograde* conduction. C *Apr 1*- regular sinus rhythm Man aged 21, *surgical* repair of atrial septal defect under hypothermia, Mar 26, atrial flutter during operation, 1 mg *digoxin* (Lanoxin) injected, no further digitalization D AV dissociation with interference *secondary* to sinus *arrhythmia* and *bradycardia*, *latent* heart block Bipolar right atrial lead from second right intercostal space and fourth left intercostal space on sternal border *with* double amplification shows upright P waves throughout Subject is at rest, first and last P waves following AV nodal beats are conducted, other beats are dissociated E After exercise; sinus is in command for four successive beats, P-R interval of conducted beats in late diastole *shortens* from 0.34 to 0.24 sec. Man aged 21, atrial septal defect and *syncopal* attacks; the latter subsided after AV *nodal automatism* became established.

"captures" may not take place. But in the same case, slight variations of the rates may produce a shift in the responsive and refractory phases, and *interference beats* may appear. Thus, the distinction of AV dissociation with or without interference is purely artificial.

The term AV dissociation is often loosely applied to AV heart block. AV heart block is due to depression or interruption of conduction, while in *AV dissociation*, the SA impulse fails to reach the ventricle because of its arrival during the normal refractory phase following a previous impulse (Katz, 1946).

Experimental Findings. Rothberger and Winterberg (1910, 1912) have shown that the development of AV nodal rhythm in dogs is preceded by a short phase in which the atria are controlled by the SA node and the ventricles by the AV node In other experiments, occasional SA impulses interfered with the ectopic pacemaker Ganter and Zahn (1912) obtained similar results. Scherf (1929) produced AV dissociation during aconitine intoxication. Luten (1925), in studies on digitalis intoxication in dogs, found that AV dissociation with a ventricular rate higher than the atrial rate preceded ventricular tachycardia. Van Bogaert (1933) arrived at similar conclusions with ouabain

Clinical Findings. Wilson (1915) was the first to recognize AV dissociation with interference, and White (1916) described two further cases, to which another was added by Hewlett (1923). It was Mobitz (1923) who coined the term *interference dissociation,* which Scherf (1926) improved to *dissociation with interference* Mobitz also gave a correct interpretation of the first case ever published but not recognized (Wenckebach, 1906) Lewis (1925) and Wenckebach and Winterberg (1927) published extensive reviews, these were brought up to date by Scherf and Schott (1953), Holzmann (1955), and Katz and Pick (1956)

Most cases were described in the course of acute rheumatic carditis, in which the incidence is about 10 per cent (Oettinger, 1935). Diphtheria (Korth and Schrumpf, 1936) and other acute infections may also cause it. Digitalis overdosage as well as acute infections were considered in the cases of Bloom and Perlow (1930), Laubry and Lequime (1933), and Laubry and Puddu (1936). Scherf and Boyd (1948) believe that dissociation with interference is rare in nondigitalized patients, but only 2 of the 12 cases of Cutts had digitalis. Quinidine sensitivity may also cause it (Linenthal et al., 1953). These factors often act in combination; simultaneous administration of quinidine and digitalis, operative trauma, anesthesia and digitalis—each was responsible in single cases of the author's series. It has also been observed with coronary heart disease and syphilitic aortitis, and exceptionally during hypertensive crises of adrenal tumors (Hegglin and Holzmann, 1937). While, in most of these cases, AV dissociation was transient, in a child of Ledoux and Arcay (1936) with a normal heart, it had been persisting for years. Since persistent AV dissociation was observed in association with atrial septal defect, it may exist as a congenital variety (Papp, 1957).

The diagnosis is made through the electrocardiogram. The clinical impression is that of atrial extrasystoles, since the interfering beats are premature and are not followed by a compensatory pause. The irregularity also disappears on effort, for SA acceleration may temporarily abolish AV dissociation. The venous pulse may show *giant waves* when atrial and ventricular contractions coincide. Coexistent SA bradycardia may cause syncope.

Electrocardiographic Patterns. The varying SA rate (if SA arrhythmia is present), the coexistence of latent or partial heart block, the tachycardia caused by an irritable AV node, the variations of the refractory period of the junctional tissues and the ventricles, the transition into AV nodal rhythm may cause most intriguing tracings of complex arrhythmias

The *common pattern* of AV dissociation with
interference is shown in Fig. 11-43A. The average
atrial rate is 90 and, therefore, slower than the
average ventricular rate at 110, there is SA ar-
rhythmia, while the AV nodal rhythm, except
for the beat following the conducted sinus impulse,
is regular. The third to eighth and last ventricu-
lar complexes are transmitted to the ventricle with
a normal P-R interval and are premature. Only P
waves falling on top of the T wave (end of the
refractory phase) are conducted. The two rates
are so aligned that no P waves fall in late diastole
and can reach the ventricle. The three conducted
beats form the only link between the SA and AV
nodal rhythms.

As soon as the SA rhythm slows, dissociation with interference appears During maximal deceleration, SA bradycardia at an average rate of 39 develops; a bigeminal rhythm consisting of a nodal escape and a conducted beat keeps the ventricular rate at 80 (Fig 11-44B). When the vagal effect subsides, SA *rhythm* is again restored (*last two cycles* of Fig 11-44C). The P waves, which appear at a distance of 0 26 to 0 37 sec after the nodal escapes, are conducted to the ventricles at a speed of 0 31 to 0 34 sec (Figs 11-43D, E, and 11-44) This may suggest a reciprocal *rhythm*. However, if the P waves are magnified through use of a right atrial lead and double amplification, it becomes evident that all P waves are upright and of SA origin, and that there is no retrograde conduction (Fig 11-43D, E). Even so, the reactivation of the SA node after the nodal escape suggests that the latter is instrumental in this, either through a mechanical effect (White, 1921, Rosenbaum and Lepeschkin, 1955) or by improvement of the circulation in the SA node If this is so, the two pacemakers also work in relay, the AV node reactivating the SA node and this then taking over the lead for a few beats until a longer SA standstill occurs which provokes a nodal escape

AV dissociation due to irritability of the AV node is rare and forms a link with paroxysmal tachycardia (Fig 11-45)

Contrary to Figs 11-43D, E, and 11-44, which show SA bradycardia, the basic disturbance is an *ectopic* atrial tachycardia at an average rate of 128 with 2:1 AV block and a P-R interval of 0 24 *to* 0.28 *sec* (Fig. 11-45, bottom row). Slight slowing of the SA rhythm produces an AV nodal [illegible], which [illegible], during [illegible]wo rates soon equalize, slight slowing of the AV *rhythm* coincides with *slowing of the SA rhythm* (Fig. 11-45, top row), until a P wave falls late enough in diastole to capture the ventricles (sixth R wave). The dissociation, however, persists, even though the AV nodal rhythm has become slow; a P wave falling late in diastole remains blocked because of coexistent AV block. The same factors which produce an irritability of the SA node act on the AV node as well, which explains the alignment of the two rates during the tachycardic phase.

The association of 2:1 AV block with AV dissociation, but without nodal irritability, has a different electrocardiographic pattern. Conducted beats here have an aberrant pattern which appears when the SA rhythm slows. The ectopic center is emerging only when the half SA rate becomes less than the autonomic rate of the ectopic center. The number of impulses discharged by the SA node is of secondary

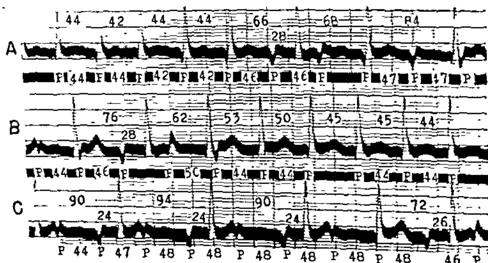


Fig 11-45 Lead II AV dissociation with "irritable" AV node. A. End of a *paroxysm with a* conducted beat AV dissociation persists The P wave before last is blocked in spite of its late *appearance in diastole* B Beginning of a nodal paroxysm with AV nodal escape (third beat) followed by gradual nodal acceleration until atrial and nodal *rates equalize* AV dissociation during paroxysm C Ectopic atrial tachycardia *with* 2 1 AV *block, P-R* interval = 0 24 to 0 28 sec (Courtesy of Sir John Parkinson)

11-43A) because of different spread of the SA impulse in the bundle. The P-R interval of the SA beats may be normal (Fig. 11-43A) or prolonged (Figs. 11-43, 11-44, 11-45). The prolongation may be due to latent heart block (long P-R interval), early conduction before complete recovery of the bundle takes place, or both. There is an inverse time relationship between the R-P period and the P-R interval of the conducted beat (Katz, 1946, Katz and Pick, 1956). The later the P wave appears in diastole, the faster is the AV conduction. In Fig 11-43E, the P waves appearing on top of, or shortly after, the preceding T wave are conducted to the ventricle at a speed of 0 30 or 0.32 sec, the P waves appearing later in diastole are conducted in 0 24 sec, which was the fastest conduction time of this patient, who had latent heart block. Latent heart block is frequently found in AV dissociation and is a predisposing factor, for impairment of forward conduction favors the development of retrograde block The distance between the conducted ventricular complex and the following AV nodal beat is usually the same as between two nodal beats, since nodal automatism is quickly restored (Figs 11-43D, E, and 11-44), but it may be shorter (Fig 11-43A) or longer.

The shortening has been explained by Scherf and Schott (1953) by the late appearance of the SA beat because of delayed conduction in the bundle (see slight aberrance in Fig 11-43A) while the nodal beat is on time. If the distance is slightly prolonged, it is due to fatigue of the conducting system; if the pause is longer and is equal to the distance between a conducted P wave and the next nodal R wave, following a conducted ventricular complex, one has to assume that *concealed conduction* (Langendorf, 1948) has taken place. This means that the sinus impulse reached the AV node, destroyed the immature AV impulse, and was blocked on its way to the ventricles, so that it did not become electrically visible. The same phenomenon was earlier described by Korth (1941) as *incomplete interference*, and explained by Schott (1937) as a sign of impaired conduction in the bundle.

AV dissociation may appear as a *passive ectopic rhythm* through SA bradycardia or SA block, it can then be temporarily abolished by exertion (Fig. 11-44A).

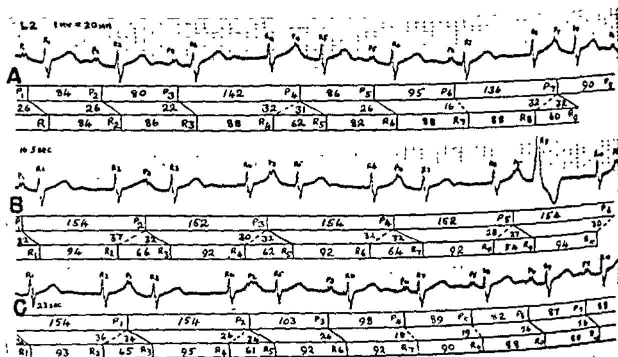


Fig. 11-44. Same case as in Fig 11-43D Lead II A. End of exercise test; after the fourth beat, incomplete AV dissociation B 16.5 sec after the end of (A). sinus bradycardia and bigeminal rhythm formed by a nodal beat and a conducted beat during maximal deceleration. R_9, which is early, shows aberrant conduction. C 23 sec after the end of (B), bigeminal rhythm gradually subsiding, conducted beats alternating with AV nodal beats in the second half of (C). Full lines, transmitted impulses; interrupted lines, no conduction. (*Permission of the British Heart Journal.*)

ectopic beats is a multiple of a *common* denominator *representing* the cycle length of the ectopic rhythm This can be easily calculated if two *extrasystoles are* seen in sequence; if they are separated from each other by longer stretches containing SA *beats, the refractory period* has to be determined on the basis of the shortest "coupling" separating the *extrasystole from* the previous *SA beat. The* latent beats have to fall within the refractory period, which may be much longer *than the* Q-T period, especially when the rate of both the SA and the ectopic pacemaker is slow An *example* is shown *in* Fig 11-46, where the SA rate is 43 and the ectopic rate is 34 The shortest "coupling" over long *stretches of records* was 0 76 sec (Fig. 11-46), all ectopic impulses following at a shorter distance after the previous SA *impulse remain* latent (interrupted vertical arrows). The parasystolic center shows more irregularity than *usually observed–the cycles* should not vary by more than 0 05 sec (Pick, 1953)–yet the varying "coupling" and the identical shape of *extrasystoles make* the diagnosis certain.

More than one parasystolic *center may* be active *simultaneously* (Holzmann, 1935); cases of atrial parasystole have also been described (Scherf and Schott, 1953). The parasystolic center may appear only *intermittently when both rates are* stable and so linked with each other that the ectopic impulses mostly fall during the refractory period. Carotid sinus *pressure* may suppress the SA rhythm, the parasystolic *rhythm remaining* in sole *control* (Mueller and Baron, 1953). *Amyl nitrite* in-

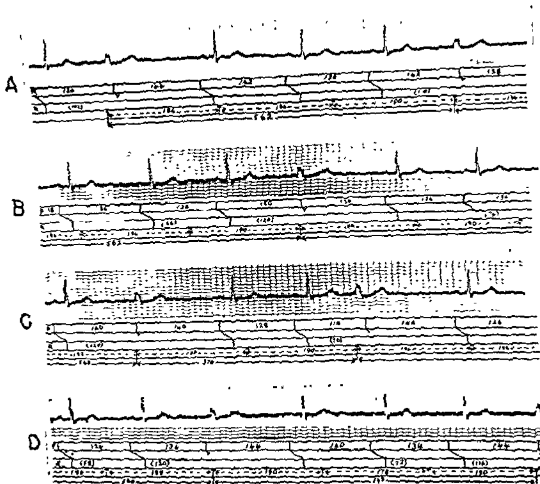


Fig 11-46. Ventricular parasystole. Continuous strip in lead II Sinus rate, 43; rate of ectopic pacemaker, 34 Shortest coupling of manifest ectopic beats (full vertical arrows), 0.76 sec. All ectopic beats falling short of this distance remain latent (interrupted vertical arrows). Horizontal interrupted lines, distances between ectopic impulses; horizontal full lines, distances between manifest ectopic impulses Woman, aged 53; coronary disease.

importance; it is the number of impulses reaching the bundle which determines the activity of the secondary pacemaker (Oettinger, 1935; Dressler et al., 1952).

Transition from AV dissociation to AV nodal rhythm is not uncommon (Fig. 11-43B); the two arrhythmias are interrelated, and the difference consists only in the presence or absence of retrograde block AV dissociation may also appear as a transient phase under quinidine treatment for atrial fibrillation before SA rhythm is established. It is often observed during acute rheumatic fever in combination with almost any arrhythmia (Bain, 1939; Vakil, 1954).

Prognosis and Treatment. *Prognosis* depends on the underlying cause. AV dissociation has little significance if it appears in a patient with otherwise healthy myocardium, but this is rarely the case. Its appearance during infections means cardiac injury, which may be slight or severe, its persistence after subsidence of rheumatic arthritis is a warning that carditis is still active Should it develop during treatment with digitalis or quinidine, the drugs should be stopped, for the disturbance is evidence of toxicity

Treatment has no place in AV dissociation. When the latter arises as a passive ectopic rhythm, it is an expression of a normal cardiac mechanism brought into play by depression of primary impulse formation Syncopal attacks due to SA bradycardia cease as soon as nodal automatism is established. If AV dissociation is due to nodal irritability, treatment should be that of paroxysmal tachycardia.

PARASYSTOLE

Parasystole, like AV dissociation, involves the concept of two simultaneously and independently acting pacemakers, one of which is in the SA node, the other usually in one of the ventricles. Such a possibility was first shown to exist by Fleming (1911) He imagined that the ectopic focus lies in "what may be called a backwater of primitive cardiac tissue" and that "physiological stimuli passing down the main channel are unable to disturb the point where ventricular stimuli arise", thus, the slower ventricular focus remains protected from the faster SA impulse. A *protective block* was assumed by Kaufmann and Rothberger (1919), who later (1922) made the first extensive study of the coexistence of two independent centers of impulse formation. In cases with ventricular rhythm faster than that of the SA pacemaker, it was thought that there might be an *exit block* which prevents the dominance of ectopic pacemaker and the transformation of parasystole into ventricular tachycardia. The term "block" applied in this sense is a misnomer, for the emphasis is not on inhibited conduction but on diminished excitability; excitability in relation to strength of the dominant rhythm determines the function of the ectopic center (Scherf and Chick, 1951).

Scherf (1927) was able to produce short periods of parasystole in dogs by mechanical and electrical stimuli after reduction of cardiac excitability with quinidine or sensitization of the heart with barium chloride and aconitine Longer-lasting parasystole, without mechanical stimulation, was produced by application of veratrine; parasystole so produced fulfilled most of the clinical criteria.

Parasystole is rare, its incidence being about 0 04 per cent of all routine ECGs recorded in a general hospital (Scherf and Boyd, 1950). It is mainly observed in coronary heart disease and is believed to be always evidence of an abnormal heart, except for the exceptional cases of nodal parasystole (Pick, 1953). Whether this belief can be upheld is questionable, since cases with normal hearts have been described (Singer and Winterberg, 1920, Heinz and Eldridge, 1957). Scherf and Schott (1953) found 11 cases without structural heart disease among 49. Most of the patients with organic heart disease were experiencing heart failure and were receiving digitalis, stopping the drug abolished the ectopic rhythm (Holzmann, 1935).

Electrocardiographic Patterns. The common electrocardiographic pattern is that of ventricular extrasystoles of identical shape. These appear at a varying distance from the SA beat and, therefore, are not induced by it, the "coupling" is variable, as opposed to the usual form of extrasystole to be observed in bigeminal rhythm. In fact the term "coupling" should not be applied, since the ectopic beats appear as cycles of an automatic rhythm, the emergence of which is regulated by the refractory phase of the dominant rhythm. When SA and ectopic impulses fall together, fusion beats result, having an intermediate shape between ectopic and SA beats. The final proof of parasystole can be given if the distance between two

ectopic beats is a multiple of a common denominator representing the cycle length of the ectopic rhythm This can be easily calculated if two extrasystoles are seen in sequence, if they are separated from each other by longer stretches containing SA beats, the refractory period has to be determined on the basis of the shortest "coupling" separating the extrasystole from the previous SA beat The latent beats have to fall within the refractory period, which may be much longer than the Q-T period, especially when the rate of both the SA and the ectopic pacemaker is slow An example is shown in Fig 11-46, where the SA rate is 43 and the ectopic rate is 34 The shortest "*coupling*" over long stretches of records was 0 76 sec (Fig. 11-46); all *ectopic impulses* following at a shorter distance after the previous SA impulse remain latent (interrupted vertical arrows). The parasystolic center shows more irregularity than usually observed—the cycles should not vary by more than *0.05 sec* (*Pick*, 1953)—yet the varying "coupling" and the *identical shape* of extrasystoles make the diagnosis certain.

More than one parasystolic center may be active simultaneously (*Holzmann*, 1935); cases of atrial parasystole have also been described (Scherf and Schott, 1953). The parasystolic center may appear only *intermittently* when both rates are stable and so linked with each *other that the ectopic* impulses mostly fall during the refractory period. *Carotid sinus pressure* may suppress the SA rhythm, the parasystolic rhythm *remaining* in sole control (Mueller and Baron, 1953). *Amyl nitrite* in-

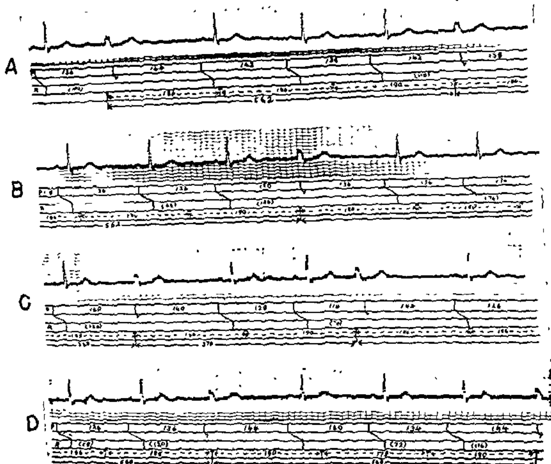


Fig 11-46. *Ventricular parasystole* Continuous strip in lead II, Sinus rate, 43, *rate of ectopic* pacemaker, 34 *Shortest* coupling of manifest ectopic beats (full *vertical arrows*), 0.76 sec. All *ectopic* beats falling short of this distance remain latent (*interrupted* vertical arrows). Horizontal *interrupted* lines, distances between ectopic *impulses;* horizontal full lines, distances between manifest ectopic impulses. Woman, *aged 53;* coronary disease.

halation may have an opposite effect through acceleration of the SA rhythm or improved blood supply (Holzmann, 1935).

Parasystole with exit block is said to exist when only some of the ectopic beats falling outside the refractory period become manifest. This usually happens in the rare cases where the rate of the ectopic centers is faster than that of the SA rhythm.

Though parasystolic rhythm should be strictly separated from bigeminal rhythm with fixed coupling, intermediate cases have been described. Holzmann believes that the same metabolic state of the cardiac muscle induced by digitalis can cause reentry and parasystole; constant coupling can be simulated by stability of the two rhythms. In the case of Mueller and Baron, coupled rhythm alternated with parasystole, and the authors believed that the ectopic impulses were not strong enough to emerge except during the supernormal phase of recovery. The reverse, i.e., the production of induced extrasystoles by the ectopic pacemaker, has also been described (Scherf and Schott, 1951) and explained by "*directional*" *block* around the ectopic center.

Parasystole is an electrocardiographic curiosity and not a clinical state, since it has no hemodynamic importance. Prognosis and treatment depend on the causative factors.

12

Cardiac resuscitation by external electric stimulation and countershock

PAUL M. ZOLL

Cardiac arrest presents a critical problem in many different clinical situations. It is a desperate emergency that requires prompt, energetic, and effective measures to effect resuscitation within the urgent time limit of about 4 min

Therapeutic procedures in the past have included cardiac puncture, intracardiac injection of drugs, and thoracotomy with cardiac massage, but the results with all these procedures are unsatisfactory in that the complete recovery rate is usually about 30 per cent (Stephenson et al , Cole)

A complicating factor in the emergency treatment of cardiac arrest is that the mechanism of the arrest may be either ventricular standstill or ventricular fibrillation. These mechanisms cannot be differentiated by the usual clinical means but only by an electrocardiogram or by direct inspection of the exposed heart, they tend to occur in somewhat different situations, however, and, most important, they require different treatment

Ventricular standstill occurs particularly in four clinical situations. (1) in the Stokes-Adams attacks which occur in patients with AV heart block; (2) during reflex vagal stimulation, as in patients with a hypersensitive carotid sinus, (3) during treatment with cardioactive drugs, such as digitalis, quinidine, and procaine amide, and (4) unexpectedly, during various diagnostic and therapeutic procedures, particularly in the operating room under anesthesia *Ventricular fibrillation* may occur in a Stokes-Adams attack, but it occurs most often as a disastrous complication of acute myocardial infarction.

The first problem to be considered in this chapter is ventricular standstill. Recently, the author has developed a new therapeutic approach to the problems posed by it. It is an externally applied cardiac pacemaker that produces effective ventricular beats, terminates ventricular standstill, and maintains an externally controlled rhythm for as long as necessary until spontaneous ventricular beats return. The electric stimulator functions like a natural intracardiac pacemaker but is under complete external control (Zoll, 1952). Figure 11-47 shows the electrocardiogram of a period of cardiac arrest terminated by electric stimuli and ventricular beats. The instrument[1] is easily applied and clinically practicable Two dials permit variation of rate of stimulation, and of amplitude of stimulation from 0 to 150 volts. Output wires carry the electric stimuli to the electrodes, which are smeared with conductive jelly and held on the precordium (usually in the V_2 and V_5 positions) by plastic handles or a rubber strap. The electric shocks go through the chest wall and produce ventricular beats This technique of external electric stimulation of the heart has now been used successfully by the author and others to resuscitate over 200 patients with Stokes-Adams attacks, 3 with reflex vagal stimulation, 4 with standstill due

[1] Manufactured by the Electrodyne Company, Norwood, Mass.

to drugs, and 8 with unexpected standstill, usually occurring during surgery (Zoll, et al., 1956a).

The first condition to be considered, Stokes-Adams attacks, occurs in patients with AV block and consists of attacks of cerebral ischemia due to very slow idioventricular rates, ventricular standstill, ventricular tachycardia, or ventricular fibrillation (Parkinson et al., 1941). The attacks are manifested by dizziness, syncope, prolonged unconsciousness, and convulsions, and they may end in death. The cardiac origin of such seizures becomes clear when cardiac arrest is observed during an attack, by the absence of a pulse or heart sounds. A more exact diagnosis is usually

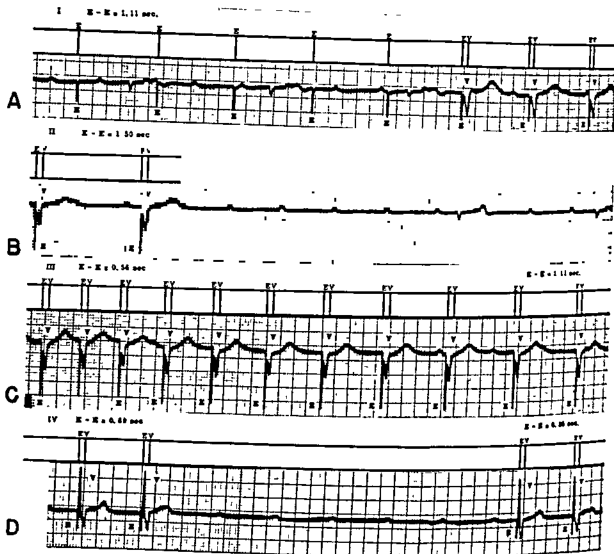


Fig 11-47. External electric stimulation in a patient with Stokes-Adams attacks. Lead aVF; standardization half-normal (1 mv equals 5 mm) A Interruption of idioventricular rhythm by faster externally paced beats The intensity of the electric stimuli, *E*, was progressively increased until ventricular responses, *V*, were produced. Three spontaneous idioventricular complexes (cycle length, 2 04 sec) occurred during ineffective stimulation; during effective stimulation at a faster rate (cycle length, 1 11 sec) they were suppressed. B. Resumption of idioventricular rhythm following external stimulation. When stimulation was stopped, the spontaneous ventricular pacemaker reappeared after a pause of 4.64 sec and regained its previous rate within three beats. C. Effective stimulation at varying rates. Each stimulus, *E*, produced a ventricular response, *V*. Each electrocardiographic ventricular response depended upon an electric stimulus, as shown by the constant relationship at widely varying rates of stimulation. D. Ventricular standstill during temporary interruption of stimulation. During a test period of 5.5 sec no stimuli were applied. No spontaneous ventricular contractions occurred during this interval, and the patient lost consciousness. Resumption of stimuli immediately gave ventricular responses, and the patient revived at once. (*Reprinted by permission of Grune & Stratton, from Circulation, 1954.*)

made by the observation of a very slow heart rate due to an idioventricular rhythm between attacks, however, *it is important to remember that evidence of any degree of AV block between attacks establishes the diagnosis and that, at times, in a patient with this disease, the pulse rate may be normal and AV conduction may be normal,* with a P-R interval of less than 0 20 sec

There are three major problems in the treatment of *Stokes-Adams attacks: (1) emergency resuscitation from a major attack,* (2) termination of persistent ventricular standstill, and (3) prevention of frequently recurrent attacks.

For a major attack with persistent syncope, emergency resuscitation must be effected promptly and the circulation to the heart and *brain must be restored within 3 or 4 min* Electrocardiographic identification of the mechanism of the attack is useful but, even when an electrocardiogram is not available, *treatment must be immediately instituted*

If the mechanism of the attack is ventricular standstill or is unknown, *the precordium should be struck forcefully* Then *cardiac puncture* should be *performed, the* tip of the needle should be embedded in the heart wall, and *the hub* of the needle should be tapped sideways *repeatedly to* stimulate ventricular beats If arrest persists, *epinephrine hydrochloride* may be injected through the needle into a *cardiac chamber,* care being taken not to put any within the myocardium

These measures should be tried in sequence *if there is delay* in applying the electric pacemaker They are *simple* and usually immediately feasible, but are frequently *ineffective* and *sometimes* produce fatal complications The *electric pacemaker,* on the contrary, is completely safe and is uniformly effective in terminating attacks due to slow idioventricular rates or ventricular *standstill* As soon as possible, therefore, the electric pacemaker should be *attached* to the patient and stimuli *of increasing* intensity *applied* until cardiac responses occur (Fig 11-47) If adequate intrinsic ventricular activity appears *following* resuscitation, *stimulation* may then be stopped However, if there is excessive delay in applying the cardiac pacemaker, *or if* the mechanism is ventricular fibrillation, these *measures* will fail

The *author* has now resuscitated *over 200* patients from Stokes-Adams attacks with the electric pacemaker In an early series of 50 cases, attacks due to *very slow idioventricular* rates were observed in 12 patients, and to *ventricular standstill* in 45 patients; *these* episodes of *cerebral ischemia* were all *terminated* immediately by electric stimulation. This dramatic effect was observed countless times Stokes-Adams attacks due to *ventricular tachycardia or fibrillation* were seen in 20 patients. It is clear that such *seizures* cannot be terminated by stimulation. However, in 8 patients with frequent attacks due to multifocal ventricular tachycardia *or fibrillation, continued external stimulation prevented* their recurrence.

If adequate intrinsic ventricular activity fails to appear *after successful* resuscitation, a new, second *problem is posed. It has heretofore* been impossible to observe ventricular standstill for more than the few minutes that life *would persist. For the first* time, we have in the *electric pacemaker a means* of producing heart beats under such *circumstances and* of maintaining life indefinitely (as long as 109 hr in *the* author's experience). With the patient kept alive by the external pacemaker, there is no *desperate emergency,* and heroic and dangerous measures are unnecessary. With careful, deliberate *infusions of diluted solutions of sympathomimetic amines,* particularly *epinephrine hydrochloride,* the author was often successful in arousing an idioventricular *rhythm,* in accelerating it to an adequate rate, i.e, *between* 30 and 45 per minute, and in maintaining it there *He also used norepinephrine* to maintain an adequate blood pressure *whenever necessary*

The *prevention of recurring attacks* is a third major problem of Stokes-Adams disease that is still largely unsolved. When the idioventricular *rate is too slow* (below *30 per minute*), *ephedrine sulfate* and *isoproterenol (Isuprel)* are often *useful* for long-term *maintenance* of heart rates *between* 30 and 45 *beats per minute.* When recurring attacks are due to *varying AV conduction, atropine, ephedrine,* and *isoproterenol* should be tried When the attacks are due to recurrent ventricular tachycardia *or* fibrillation, *ephedrine* and *isoproterenol again,* or the cardiac pacemaker, *may* be useful in *reducing* ectopic activity *by increasing* the basic ventricular rate;

quinidine and *procaine amide* are contraindicated in these patients with heart block and Stokes-Adams disease.

It is for this reason that a clear distinction should be made between patients with AV block who have Stokes-Adams attacks and patients without AV block who may have disturbances of ventricular rhythm. Episodes of ventricular arrhythmias that cause cerebral ischemia in the latter patients should not be called Stokes-Adams attacks but rather *cardiac syncope*, a much more general term. In them, there is no contraindication to quinidine and procaine amide.

Despite all the author's efforts and this new approach, many of the patients have died of Stokes-Adams attacks. These fatalities occurred because the electric pacemaker was not applied during a fatal attack when the episode occurred unexpectedly; because the attack was due to ventricular tachycardia or fibrillation and was not terminated by the electric pacemaker; or because of irreversible cerebral damage due to delay in applying electric stimulation. Several patients died of complications of their Stokes-Adams disease or of other primary disease, such as acute myocardial infarction, acute bacterial endocarditis, cardiac tamponade from multiple cardiac punctures, and congestive heart failure

Episodes of cerebral ischemia due to *ventricular standstill or fibrillation also occur in* patients without Stokes-Adams disease Certain of these episodes, as in the carotid sinus syndrome, are usually transitory, and are clearly due to reflex vagal stimulation The distinction between Stokes-Adams attacks and reflex vagal standstill is of clinical importance because of differences in the course, prognosis, and treatment of each condition. Again, this distinction is usually simple but ultimately depends upon the presence or absence of AV block at any time between attacks

External electric stimulation was repeatedly effective in resuscitating three patients with ventricular standstill due to reflex vagal stimulation. In all of them, episodes of ventricular arrest repeatedly interrupted normal sinus rhythm abruptly, producing syncope and convulsions. The precipitation of such episodes by carotid sinus pressure and their disappearance following the administration of *atropine sulfate* established their reflex vagal origin. More than 100 times, in these patients, external electric stimulation terminated ventricular standstill and restored an effective circulation

A third type of cardiac arrest occurs as a result of *depression of cardiac automatism* due to drugs. The author has observed three patients with attacks of syncope due to digitalis. With digitalis toxicity, SA block occurred, whereupon cardiac activity was maintained by nodal or ventricular pacemakers, intermittent failure of these pacemakers resulted in periods of ventricular standstill lasting as long as 1 min. External electric stimulation resuscitated the patients several times. With recession of the digitalis effect, the seizures stopped.

Two patients with ventricular standstill following intravenous administration of procaine amide in the treatment of ventricular extrasystoles and tachycardia, have also been resuscitated promptly by other workers by means of the external electric pacemaker.

Cardiac arrest may also occur in a fourth group of patients. Young, healthy, individuals without heart disease may develop cardiac arrest unexpectedly, while undergoing various diagnostic and therapeutic procedures, particularly while *under anesthesia* in the operating room. Though infrequent, each such accident is a dreadful catastrophe.

The commonly recognized mechanisms of unexpected arrest are ventricular standstill or *fibrillation, standstill is the* usual cause, occurring probably about 90 per cent of the time, and reflex vagal stimulation appears to be a frequent precipitating factor.

Electric stimulation of the heart has been effective in 11 such cases of unexpected cardiac arrest Three of these patients were observed by the author personally. The others were described to him in personal communications by the physicians concerned The cases occurred during various procedures, 10 during surgery, 1 during pericardiocentesis The cardiac arrest was terminated in each case by the electric pacemaker, so that thoracotomy and cardiac massage were not necessary. Eight of the 11 patients recovered completely; 2 died of unsuccessful cardiac surgery, and 1 died 5 hr after an abdominal operation

The author's experiences with the cardiac pacemaker indicate that external electric stimulation can resuscitate the heart from arrest that occurs unexpectedly under anesthesia during

surgery or other procedures, just as it does from the other types of cardiac arrest The technique has been applied safely in the operating room within the few minutes available for complete resuscitation. It seems to us, therefore, that external electric stimulation of the heart should be tried quickly, *even in the operating room*, before resorting to thoracotomy and cardiac massage.

In addition to these successful experiences, the author has personally attempted resuscitation with the cardiac pacemaker unsuccessfully in several patients who developed unexpected cardiac arrest, most, but not all, of them during anesthesia A brief list of the procedures involved indicates their wide variety and frequently insignificant nature They include jugular puncture, intravenous pyelography, bronchography, cardiac catheterization, endotracheal intubation, hip nailing, cholecystectomy, and thoracic and cardiac surgery In a few, the circulatory arrest was due to ventricular fibrillation, and stimulation was ineffective In all the others, electric stimulation was applied too late, over 5 min after onset of arrest, and usually after prolonged, ineffective massage

These failures emphasize two critical problems of unexpected cardiac arrest First, the responsiveness of the heart to stimulation diminishes progressively with continued anoxia Second, effective ventricular beats *cannot* be stimulated by the pacemaker during ventricular fibrillation The time interval between arrest and the resumption of effective ventricular output must be brief, probably less than 3 or 4 min, if cerebral and cardiac function is to return unimpaired Avoidance of excessive delay depends upon immediate recognition of the cardiac arrest and then the immediate application of external stimulation and institution of a *prearranged* program for resuscitation

Immediate recognition of arrest at its onset depends upon continuous monitoring of cardiac activity The author has developed a practical *monitoring device*[2] combined with the pacemaker, and has used it to great advantage in the operating room and in patients with recurring Stokes-Adams attacks, to signal immediately the cessation of heart beats.

[2] Manufactured by the Electrodyne Company, Norwood, Mass.

Briefly, the monitor amplifies the electric activity of the heart like an electrocardiogram, so that patient contact and pickup of impulse are not difficult, it gives *an audible as well as a visual signal of each beat*, so that undivided attention to the monitor is not needed, and *it rings a compelling alarm* with the onset of arrest. Furthermore, it shows the mechanism of the arrest promptly, so that there is no problem in *differentiating ventricular standstill from fibrillation* If standstill is seen, stimulation with the pacemaking half of the machine can be effected without delay through the same electrodes on the chest. Ideally, perhaps, such a monitor-pacemaker should be applied routinely to all patients under anesthesia Certainly the monitor-pacemaker should be applied beforehand to all patients undergoing anesthesia who present a particularly high risk of cardiac arrest. This specially vulnerable group includes patients with extreme debility, severe heart disease of any kind, AV block of any degree, patients receiving large doses of quinidine or procaine amide, patients with high serum potassium, patients with a sensitive carotid sinus, patients undergoing surgery involving the extraocular muscles, and particularly patients who have had previous episodes of cardiac arrest.

Immediately upon recognition of arrest, a rehearsed program of treatment should be instituted. The heart *should be stimulated* mechanically by striking the precordium forcefully, by cardiac needle puncture, or by cardiac manipulation through the diaphragm, if the abdomen is open These measures are simple and immediately feasible and are worth the few seconds necessary because they are occasionally *effective*. If no time has been lost in the recognition of arrest, it is proper to spend no more than 1 min in attaching and trying the cardiac pacemaker. This trial, which should be successful in most cases of ventricular standstill, can be made easily within this time limit if the electric pacemaker is close at hand and if the operating room personnel have been trained in its use by previous emergency drills

If the initial mechanism of cardiac arrest is ventricular fibrillation or if the patient is not resuscitated by external mechanical or electric stimulation, the chest must be opened promptly and cardiac massage begun. At the

same time the anesthetist must provide adequate respiratory exchange of oxygen. Once blood is being squeezed out of the heart by the surgeon's hand, the desperate urgency of the 3-min time limit is over and further measures can be undertaken, if necessary, with more care and deliberation.

If the ventricular fibrillation appears or persists in spite of effective massage, *defibrillation* should be attempted only after the myocardium becomes pink and firm, *countershock* with a 60-cycle alternating current of 120 to 150 volts for 0.15 sec applied across large electrodes on the heart is most effective for this purpose.

Ventricular standstill may persist despite effective massage or may recur following defibrillation. *Epinephrine hydrochloride* (1 ml of a 1:10,000 dilution) may be injected into the left atrial chamber and may be repeated in 3 min if necessary. If standstill continues and the myocardium is flabby, 5 ml of 10 per cent *calcium chloride* may be given. For persistent standstill, the electric pacemaker may be applied directly to the heart with a special bipolar electrode, so that massage need not be continued too long.

If resuscitation is successful, the patient should be kept under constant observation for 2 or 3 days, because arrest frequently recurs. The cardiac monitor-pacemaker is most useful in providing continuous information about cardiac activity during this time and in providing immediately available, effective resuscitation from standstill. In the last year we have saved two patients from recurrent arrest in this way.

The second mechanism by which cardiac arrest may occur is *ventricular fibrillation*. Countershocks of 60-cycle alternating current of 50 to 150 volts and for 0.1 to 0.2 sec applied across the exposed heart have been used for some time as an adjunct to cardiac massage to stop ventricular fibrillation. Recently the author and others have used similar countershock current of higher voltage experimentally to stop ventricular fibrillation by applying it *externally* across the unopened chest (Guyton et al.). The author has applied such high-voltage countershocks repeatedly in the experimental animal without producing damage to the heart, nervous system, or skin.

Furthermore, he found that externally applied countershock would also terminate atrial fibrillation, atrial tachycardia, nodal tachycardia, and ventricular tachycardia as well as ventricular fibrillation. The efficacy of the external countershock was clearly established by the repeated observation of the instantaneous cessation of these arrhythmias upon application of the electric current (Zoll, 1956c).

After these successful experimental observations, this technique was applied to ventricular fibrillation in man (Zoll, 1956b). The author has now stopped ventricular fibrillation twenty times in 11 patients. However, all but 1 of these patients died. In each fatal instance the countershock was applied after considerable delay (5 min or more), and effective beats did not return after defibrillation. It was recognized beforehand in most of these cases that the procedure had little chance of saving the patient because of the long delay. The underlying causes of fibrillation in these cases were acute myocardial infarction, digitalis intoxication, and Stokes-Adams attacks.

One patient survived. He had active Stokes-Adams attacks and was resuscitated from many episodes of ventricular standstill by the electric pacemaker, and from three episodes of ventricular fibrillation by external countershocks of 270 to 360 volts. In each instance the countershock was applied within 3 or 4 min after the onset of the fibrillation. Ventricular standstill occurred after each defibrillation, but external electric stimulation then evoked effective ventricular beats, which were followed shortly by an intrinsic ventricular rhythm and complete recovery. Figure 11-45 shows the electrocardiograms taken during one of these episodes. In the last year, the author has successfully resuscitated 8 patients over 400 times from ventricular tachycardia or fibrillation by external electric countershock.

The termination of atrial fibrillation, supraventricular tachycardia, and ventricular tachycardia by external countershock, in addition to the possibility of external defibrillation, has wide clinical potentialities that have not been completely explored. This technique may prove useful in desperate cases resistant to drug therapy, by providing a means of immediate termination of the arrhythmia without the dangers of prolongation of the arrhythmia and in those connected with massive drug administration.

The demonstrated efficacy of external coun-ershock in stopping ventricular fibrillation in ian provides a readily available and safe tech-ique for stopping this usually fatal arrhythmia. utside the operating room and in seriously l patients in whom thoracotomy and cardiac iassage may be particularly inadvisable, ex-ernal countershock may offer the only ef-ective therapy. In the operating room, con-inuous cardiac monitoring, immediate external lectric stimulation, and external electric de-ibrillation make up a combined technique oy which unexpected cardiac arrest may be ecognized promptly, and the patient may be esuscitated from ventricular standstill or fi-orillation, before resorting to the more for-midable and traumatic procedure of cardiac massage

The major difficulty with external electric cardiac stimulation is that the electric shocks which stimulate ventricular responses are often very painful. Although this pain is not impor-tant in the emergency resuscitation of an un-conscious patient from cardiac arrest, it is often very distressing when patients require prolonged or repeated stimulation for repeti-tive seizures, persistent absence of intrinsic ventricular beats, excessively slow idioven-tricular rates, or prevention of recurring ven-tricular tachycardia or fibrillation. These prob-lems arise most in patients with Stokes-Adams disease, whether it occurs naturally from car-diac disease or whether it follows cardiac sur-gery, particularly the repair of interventricular septal defects.

Several approaches to this problem of pain with stimulation have been developed. In the first place, analgesic agents like meperidine (Demerol) often make the pain more tolerable. Furthermore, careful application of the elec-trodes to the chest wall with moderate rub-bing of the skin may lower the threshold for

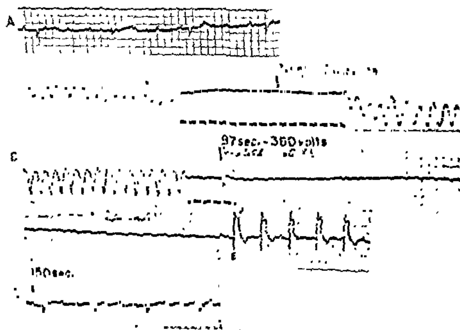


Fig 11-48 Resuscitation from ventricular fibrillation in a patient with Stokes-Adams attacks. Lead aVF, amplification half-normal (1 mv = 5 mm). A. Patient's usual idioventricular rhythm before seizure B Ventricular fibrillation that persisted after application of countershock of 300 volts The indicated times are from the beginning of the continuous electrocardiogram, 1 min after the episode began The broken line indicates when the electric activity of the heart was not being recorded ("instomatic" switch turned on) C. The two strips are continuous External countershock of 360 volts at 87 sec terminated the arrhythmia and produced ventricular stand-still External electric stimuli, E, at 60 volts produced ventricular beats, V, 12 sec later. D. Re-sumption of usual idioventricular rhythm within a few seconds after termination of electric stimulation. The patient regained consciousness promptly and recovered completely. (From Zoll, New England J. Med 1956)

stimulation with consequent reduction in the amount of pain.

A second approach has proved most useful in the management of atrioventricular block and cardiac arrest that follow cardiac surgery and constitute a major complication of open-heart surgery. *A modification of the technique* of external electric stimulation of the heart was introduced (Weirich et al., 1958), by *stimulating the heart directly* with an electric pacemaker. At the time of surgery, a wire is inserted into the myocardium and brought through the skin, where it is attached to an electric stimulator, and a second wire from the pacemaker is placed subcutaneously to complete the electric circuit. Effective cardiac stimulation is possible by way of the myocardial electrode at voltages (usually well below 10 volts) that do not produce any pain or skeletal muscular movement. This type of direct cardiac stimulation can be used freely and most effectively in the management of postoperative heart block for several weeks after surgery; in most instances, during this time, normal sinus rhythm returns and the difficulty is completely solved. In addition to the requirement of open thoracotomy to place the electrode, this technique does have two limitations. Infection may occasionally occur at *the site of exit of the wires through the skin.* Secondly, stimulation via the myocardial electrode becomes ineffective, usually within 8 weeks or less, apparently because of inflammatory reaction about the myocardial electrode. These difficulties make this method unsuitable for the long-term management of patients with Stokes-Adams disease.

Two interesting modifications of Lillehei's direct myocardial stimulation have been introduced to obviate the necessity for thoracotomy. One has been the introduction of a myocardial electrode by Thevenet et al. (1958) through a blind percutaneous puncture. This technique carries with it the risk and uncertainty of a blind puncture of the heart plus the original *limitations of cutaneous infection* and ultimate ineffectiveness of stimulation within a month or two.

The second modification, by Furman and Schwedel, is the introduction of an *intracavitary wire electrode* by way of a cardiac catheter passed up a vein of the forearm into the right ventricle. Direct cardiac stimulation at voltages less than 10 volts without pain was carried out by him in one patient with Stokes-Adams disease for over 3 months. Local skin infection is a problem with this technique also, but effective stimulation is apparently possible for longer periods than with the myocardial electrode. The additional possible complications of thromboembolism and trauma to the right-sided endocardium or valves were not encountered; anticoagulant therapy was maintained throughout the entire period of stimulation. This procedure is clearly most useful in patients with Stokes-Adams disease with persistent seizures, who cannot tolerate external electric stimulation. Under these circum*stances, the risks of the* procedure are clearly acceptable. It is equally clear, however, that this technique cannot be used indefinitely for the permanent maintenance of patients with Stokes-Adams disease throughout their lifetime. Better techniques of management, by pharmacologic agents or by electronic pacemakers that may be buried in the body and operate effectively and indefinitely, are under investigation for this ultimate goal.

13

Clinical differentiation of cardiac arrhythmias

RUSTOM JAL VAKIL

Nomenclature. The term *normal sinus rhythm* implies a regular rhythm of from 60 to 100 beats per minute, initiated at the SA node. Any deviation from normal has been referred to as *cardiac arrhythmia*, irrespective of whether the abnormal rhythm was regular or irregular. Such a procedure of labeling a perfectly regular rhythm, such as that of complete heart block, paroxysmal tachycardia, sinus bradycardia, or atrial flutter, as "cardiac arrhythmia" is definitely unscientific. Hence, arises the need for more scientific designations, such as abnormal heart rhythms, abnormal cardiac mechanisms, disorders of the heart rhythm, or dysrhythmias.[1]

Importance of Abnormal Heart Rhythms. Abnormal heart rhythms are of clinical importance for several reasons: (1) their incidence is high in clinical practice, (2) they are a source of anxiety to both patient and doctor, (3) they often focus attention on the correct diagnosis of the disease, (4) their diagnosis is often an essential prerequisite to successful treatment, (5) they may predispose to complications or untoward events, (6) they may alter the prognosis or outlook of an existing cardiac condition, and (7) their prompt treatment may postpone or avoid the occurrence of cardiac failure.

[1] In order to avoid this confusing terminology, Luisada (1948) suggested dividing these disturbances into (*a*) tachycardias, (*b*) bradycardias, and (*c*) arrhythmias. The complex of these disturbances he called "disturbances of the heart rate and rhythm."

Anatomicophysiologic Considerations. From early embryonic life until death, the conducting system of the heart has the power of automatic and rhythmic contraction. The conducting system is a specialized neuromuscular tissue, endowed with the power of initiating and conducting cardiac impulses.

The heart beat is normally initiated by the SA node, which, in normal conditions, has an inherent rate of stimulus formation greater than that of any other component of the conduction system. It is, therefore, referred to as the pacemaker of the heart; in the event of its being depressed or diseased, a subsidiary or secondary pacemaker takes over the function of initiating beats (nodal or idioventricular pacemaker).

CLASSIFICATION

Many different classifications of cardiac arrhythmias have been proposed from time to time, with alleged advantages, and later abandoned in favor of new ones. On the basis of the mechanisms involved, abnormal cardiac rhythms were classified into two major groups, viz., (1) *disturbances of impulse formation* (inclusive of various types of sinus or normotopic and ectopic or heterotopic rhythms), and (2) *disturbances of impulse conduction* (inclusive of sinoatrial, atrioventricular, and intraventricular blocks) by Vakil and Golwalla (1952).

The following classification of abnormal cardiac mechanisms or rhythms, recently proposed by the American Heart Association and based

stimulation with consequent reduction in the amount of pain.

A second approach has proved most useful in the management of atrioventricular block and cardiac arrest that follow cardiac surgery and constitute a major complication of open-heart surgery. A modification of the technique of external electric stimulation of the heart was introduced (Weirich et al., 1958), by *stimulating the heart directly* with an electric pacemaker. At the time of surgery, a wire is inserted into the myocardium and brought through the skin, where it is attached to an electric stimulator, and a second wire from the pacemaker is placed subcutaneously to complete the electric circuit. Effective cardiac stimulation is possible by way of the myocardial electrode at voltages (usually well below 10 volts) that do not produce any pain or skeletal muscular movement. This type of direct cardiac stimulation can be used freely and most effectively in the management of postoperative heart block for several weeks after surgery, in most instances, during this time, normal sinus rhythm returns and the difficulty is completely solved. In addition to the requirement of open thoracotomy to place the electrode, this technique does have two limitations Infection may occasionally occur at the site of exit of the wires through the skin. Secondly, stimulation via the myocardial electrode becomes ineffective, usually within 8 weeks or less, apparently because of inflammatory reaction about the myocardial electrode. These difficulties make this method unsuitable for the long-term management of patients with Stokes-Adams disease

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cardia most often occur in subjects under 40 *years of age,* those of ventricular tachycardia are more common after 40. Complete heart block, although usually found in persons over 50, may be noted in childhood, when its origin *is congenital, diphtheritic,* or rheumatic. Pre- [illegible] may occur at any age, although [illegible]

[illegible] mitral disease or thyrotoxicosis, is more common [illegible] females [illegible]

[illegible] bladder disease, *chronic* gastrointestinal disorder, or renal calculus is in favor of extrasystole. A history of coronary occlusion or precordial pain suggests the possibilities of ventricu*lar extrasystoles, ventricular tachycardia,* or AV block.

DRUGS AND ADDICTIONS Overdigitalization may provoke extrasystoles, *especially with a bigeminal type of sinus bradycardia,* sinus arrhythmia, or AV block. Long-standing or excessive administration of epinephrine or ephedrine for bronchial asthma, *of thyroid extract for obesity,* or of atropine, quinidine, or barium chloride may elicit extrasystoles, sinus tachycardia, or AV block. Excess of tea, coffee, or tobacco may be *responsible* at times for troublesome arrhythmias.

Specific Interrogation. PRECIPITATING FACTORS Ventricular extrasystoles, heart block, ventricular tachycardia, *and sinus tachycardia* are common after myocardial infarction, sinus bradycardia, sinus tachycardia, and disturbances of conduction are often *observed during* or after diphtheria, *influenza,* pneumonia, mumps, *or jaundice.* Extrasystolic beats and paroxysms of supraventricular tachycardia may accompany gastrointestinal or emotional *disorders.*

ONSET The *onset of arrhythmia* is dramatically *sudden* or instantaneous in paroxysmal tachycardia (especially supraventricular), *it is* gradual in sinus tachycardia, *and at times in* ventricular tachycardia, *in the last,* it may be preceded by premature contractions.

ASSOCIATED SYMPTOMS An abnormal *cardiac* rhythm may be asymptomatic *or may* be associated with one or more symptoms. Palpitation is the most *common* symptom of all and is frequently noted with *extrasystoles,* atrial fibrillation, paroxysmal tachycardia, and *sinus tachycardia.* A disagreeable thump or thud, when described after a *pause, suggests a postextrasystolic* beat. Episodes of *convulsions, associated* with loss of consciousness and cyanosis *(Stokes-Adams* attacks), *are suggestive of* AV block. *Polyuria,* or frequency *during attacks,* suggests paroxysmal tachycardia. Yawning, sighing, and a feeling of exhaustion are commonly *associated with the sinus tachycardia* of neurocirculatory asthenia and cardiac neurosis. A sense of fullness in the neck, occurring *intermittently, is an uncommon* manifestation of extrasystolic beats and is due to regurgitation of blood from the right atrium to the jugular veins. *Dizziness or faintness may occur during* attacks of paroxysmal tachycardia or "runs" of extrasystolic beats. Severe precordial pain may arise during a prolonged attack of *paroxysmal* tachycardia.

TERMINATION OF ATTACK. The termination of attacks *is* gradual in *sinus rhythms and is usually sudden in paroxysmal* supraventricular tachycardia. When an attack *is* stopped by stooping or bending down, holding of the breath, or *mechanical stimulation of the vagus nerve,* supraventricular paroxysmal tachycardia is likely.

Pulsatory Phenomena. HEART RATE. *Since in extrasystoles or atrial fibrillation* some pulses may be too feeble to be transmitted to the radial artery, the heart rate *must be determined* by auscultation at the apex, not at the wrist. Cardiac rates of below 40 beats per minute suggest either complete or severe *incomplete* AV block or nodal rhythm; regular rates of over 160 *favor paroxysmal tachycardia.* Sinus tachycardia and atrial flutter are usually associated with rates below 160 per minute. A persistent, regular, and *unvarying cardiac* rate of about 150 *per minute,* particularly in an elderly *subject,* suggests a 2:1 atrial flutter.

PULSE DEFICIT. When the *cardiac* rate, determined at the apex, exceeds that of the radial *pulse* rate by 10 beats or more, a diagnosis of atrial fibrillation is justified. A pulse deficit, however, may also arise with ventricular extrasystoles, provided the pulses of the ectopic beats are too feeble to be conveyed to the radial pulse.

JUGULAR PULSE. *Neck* vein pulsations are of great diagnostic value, especially when studied *in conjunction* with the arterial pulse. For in-

on the site of origin and nature of the mechanism involved, has been more or less universally accepted of late:

ABNORMAL CARDIAC MECHANISMS OR RHYTHMS

1. Sinus Mechanisms
   - 1.1 Sinus Tachycardia
   - 1.2 Sinus Bradycardia
   - 1.3 Sinus Arrhythmia
   - 1.4 Sinus Arrest (Sino-atrial Block, Sinus Pause)
2. Atrial Mechanisms
   - 2.1 Atrial Premature Systole
   - 2.2 Atrial Tachycardia
   - 2.3 Atrial Flutter
   - 2.4 Atrial Fibrillation
   - 2.5 Wandering Pacemaker
3. Atrioventricular (A-V Nodal Mechanisms)
   - 3.1 Atrioventricular (A-V) Nodal Premature Systole
   - 3.2 Atrioventricular (A-V) Nodal Rhythm
   - 3.3 Atrioventricular (A-V) Nodal Tachycardia
   - 3.4 Atrioventricular (A-V) Nodal Escape
   - 3.5 Supraventricular Tachycardia
4. Ventricular Mechanisms
   - 4.1 Idioventricular Rhythm
   - 4.2 Ventricular Escape
   - 4.3 Ventricular Premature Systole
   - 4.4 Ventricular Tachycardia
   - 4.5 Ventricular Fibrillation
5. Parasystole
   - 5.1 Atrioventricular (A-V) Dissociation with Interference
   - 5.2 Other Parasystolic Rhythms
6. Mechanisms of Undetermined Origin
   - 6.1 Premature Systole of Undetermined Origin
   - 6.2 Tachycardia of Undetermined Origin
7. Atrioventricular (A-V) Conduction
   - 7.1 Incomplete A-V Block (Prolonged A-V Conduction Time)
   - 7.2 Incomplete A-V Block with Dropped Beats
   - 7.3 Complete A-V Block
8. Intraventricular Conduction
   - 8.1 Delayed Intrinsicoid (RS) Deflection, Left
   - 8.2 Delayed Intrinsicoid (RS) Deflection, Right
   - 8.3 QRS Interval, Prolonged
   - 8.4 QRS Interval, Prolonged, Intermittent
   - 8.5 Bundle-branch Block, Left
   - 8.6 Bundle-branch Block, Right
   - 8.7 Intraventricular Block, Unclassified
   - 8.8 Intraventricular Block, Intermittent
   - 8.9 Anomalous Atrioventricular Excitation

STUDY OF ARRHYTHMIAS

Nowhere, in the entire field of cardiology, has electrocardiography been exploited to greater advantage than in the interpretation of cardiac arrhythmia. The exact mechanism of many a hitherto obscure irregularity of the heart has been unraveled by resort to this method of instrumental investigation. Although the prime role of electrocardiography in the diagnosis of abnormal cardiac rhythms and its unquestioned superiority over other methods of examination have been securely established in recent years, the informative value of a good history and thorough clinical examination in the understanding of cardiac arrhythmias has not been sufficiently appreciated. Since the subject of electrocardiographic interpretation of cardiac irregularities has been dealt with at great length in various chapters of Vol III of *Cardiology*, the present paper deals with the clinical differentiation only. The majority of cardiac arrhythmias, as a matter of fact, are clinically recognizable, provided a systematic method of cross examination or history taking and thorough physical examination are undertaken.

The following scheme of investigation, having proved valuable in the majority of cases, is recommended for routine adoption:

- I. History
  - *A.* General (age, sex, predisposing factors, etc.)
  - *B.* Specific (regarding the various characteristics of the cardiac arrhythmia itself, e.g., onset, duration, associated symptoms and cessation of attack)
- II. Physical examination
  - *A.* Observations of pulsatory phenomena
    1. Cardiac rate and rhythm
    2. Arterial pulse
    3. Venous pulsations
  - *B.* Examination of the heart
    1. Presence or absence of organic heart disease
    2. Apex beat
    3. Heart sounds
  - *C.* Special methods of clinical examination
    1. Effect of exercise
    2. Effect of deep respiration and of apnea
    3. Effect of carotid sinus pressure
    4. Levine's method
  - *D.* Examination of other systems
- III. Instrumental investigation
  - *A.* Fluoroscopy
  - *B.* Electrocardiography
  - *C.* Phonocardiography

General Interrogation. AGE. While certain arrhythmias, such as sinus arrhythmia, paroxysmal supraventricular tachycardia, and atrial ex[illegible] trasystoles, are common in the young, paroxysmal ventricular tachycardia, ventricular extrasystoles, and atrial flutter show a predilection for elderly subjects. Sinus arrhythmia is common in infants, children, and the aged. Attacks of supraventricular paroxysmal tachy-

breath may remove the irregularity of sinus arrhythmia, bring out latent extrasystoles, and help in the differentiation of pulsus paradoxus from pulsus alternans.

CAROTID SINUS STIMULATION. COMPRESSION OF THE EYEBALLS. These maneuvers have no effect on ventricular rate in complete heart block, atrial fibrillation, or ventricular tachycardia, they tend to cause further slowing of the heart rate in incomplete AV block, they frequently terminate an attack of paroxysmal supraventricular tachycardia, they bring about a gradual and transitory slowing of the heart rate in sinus tachycardia, they may cause a sudden halving of the rate in atrial flutter, even though, in most cases, they have only a moderate and temporary effect, particularly if there is variable block.

LEVINE'S METHOD "Tapping of the foot in rhythm with the heart" has been recommended by Levine as a useful method of differentiating supraventricular from ventricular tachycardia (even a slight irregularity of rhythm favoring the latter), atrial from ventricular extrasystoles (the postextrasystolic pause being strictly compensatory in the latter), SA from partial AV block (the pause, in the latter, does not correspond in length to two cardiac cycles), and atrial fibrillation from multiple extrasystoles (all pauses in the latter are preceded by small and rapid pulsations, i e , premature beats)

Instrumental Investigations. FLUOROSCOPY Fluoroscopy may afford diagnostic clues in arrhythmias Rapid and irregular undulations of the atria without proper contractions may be observed in atrial fibrillation Synchronous contraction of the atria and ventricle, with additional contractions of the atria during the long diastolic pauses, is suggestive of *AV block*. In atrial flutter, rapid and regular *contractions of* the atria may be visible in the right anterior oblique position

ELECTROCARDIOGRAPHY This method is capable of supplying information of immense diagnostic value and should be employed in every single case of cardiac arrhythmia; however, in many cases it serves only to confirm or exclude the diagnosis, after all clinical sources of information have been fully used.

CLINICAL CLASSIFICATION OF CARDIAC ARRHYTHMIAS

The following eight types of cardiac arrhythmias are recognizable clinically, on the basis of rhythm, rate, and perceptibility of cardiac pulsation (Vakil, 1954)

1. Regular rhythm with slow rate (rhythmic bradycardia)
2. Regular rhythm with rapid rate (rhythmic tachycardia)
3. Regular rhythm with normal rate
4. Regular rhythm with unequal force of beats
5. Irregular rhythm with slow rate (arrhythmic bradycardia)
6. Irregular rhythm with rapid rate (arrhythmic tachycardia)
7 Irregular rhythm with normal rate
8 Clinically silent (imperceptible) rhythm

Type I: Regular Rhythm with Slow Rate (1) Sinus bradycardia, (2) nodal rhythm, (3) incomplete (2:1 or 3:1) AV block, (4) complete AV block, (5) atrial flutter with 4:1 or 5:1 block, (6) atrial fibrillation with nodal rhythm.

A clinical diagnosis is possible, in the majority of cases, by simultaneous study of radial artery and jugular vein pulsations, and by palpation and *auscultation of the heart.*

Type II: Regular Rhythm with Rapid Rate. (1) Sinus tachycardia, (2) paroxysmal supraventricular tachycardia, (3) paroxysmal ventricular tachycardia, (4) 2:1 type of atrial flutter, (5) preexcitation (Wolff-Parkinson-White) syndrome.

A clinical diagnosis is facilitated by paying attention to the following features: (*a*) past history of similar attacks, (*b*) mode of onset of arrhythmia, (*c*) mode of termination, (*d*) duration of attack, (*e*) rate of beating, (*f*) rhythm, (*g*) venous pulsations of the neck, (*h*) influence of exercise, respiration, carotid sinus pressure, and posture.

Type III. Regular Rhythm with Normal Rate. A *regular rhythm* with a normal rate of 70 to 80 beats per minute need not necessarily imply a *normal* sinus rhythm, as certain pathologic mechanisms are compatible with such a state. (1) first-*degree AV block*, with increased AV conduction time, (2) intra-atrial block, (3) intraventricular *conduction* defect, such as bundle branch block or arborization block, (4) paroxysmal tachycardia (*usually* supraventricular) with 2:1 block, (5) atrial flutter with 4:1 block, (6) *nodal rhythm,* when the cardiac rate is not *unduly slow*, (7) complete AV block (rarely) with *unusually high* idioventricular rate (*e g*, *congenital or diphtheritic*), (8) sinus tachycardia, with *alternating* block (either SA or AV block).

Electrocardiography is usually essential for diagnosis of this group of cases

Type IV: Regular Rhythm with Unequal Force of Beats. (1) Pulsus *alternans*, (2) pulsus paradoxus, (3) regularly alternating *extrasystoles*.

Clinical diagnosis is usually possible on the basis of "spacing" of the beats.

stance, in *sinus rhythm*, normal a, c, and v waves are seen, together with a characteristic systolic collapse of the jugular vein synchronous with each heart beat. On the other hand, in *nodal rhythm*, there is a large systolic pulsation or wave with each beat, because of simultaneous contraction of the right atrium and ventricle. In the *first-degree AV block*, with increased P-R interval, a characteristic delay occurs between the a and the c-v waves of the venous pulse; in *partial heart block*, a number of a waves are visible between the other waves and the degree of block can be determined by counting the ratio of a waves to radial pulses. In *complete heart block*, besides the phenomena of extra a waves, there are occasional large venous pulsations (familiarly known as "cannon waves"), owing to simultaneous contraction of atria and ventricles. In atrial fibrillation, even with slow rates, the absence of a waves reveals the diagnosis. In *atrial flutter*, typical, rapid, regular waves are visible during the diastolic pauses. Multiple and frequent extrasystoles can be differentiated from atrial fibrillation because the systolic collapse of the vein that occurs in the latter tends to decrease or disappear in the former.

Examination of the Heart. *Sinus bradycardia, sinus arrhythmia,* and *sinus tachycardia* are [illegible] tions and *paroxysmal supraventricular tachycardia* are more often associated with normal hearts than with diseased ones Diseases of the gastrointestinal and biliary tracts may induce reflex extrasystoles. *Paroxysmal ventricular tachycardia* seldom occurs except with severely damaged hearts *Atrial fibrillation* may be connected with mitral stenosis, coronary sclerosis, or hyperthyroidism, in the latter case, fibrillation tends to be paroxysmal. In rheumatic fever, first-degree heart block is common and is of diagnostic significance. Diphtheria may cause a varying degree of AV block. Atrial flutter and heart block may be associated with congenital heart disease. A high systolic and a low diastolic pressure is usual in complete heart block.

CHARACTER OF APEX BEAT. Palpation of the cardiac apex may suggest the existence of bundle branch block in the event of a bifid or double thrust, and of pulsus alternans in the event of alternately vigorous and feeble pulsations. Detection of a displaced apex beat or thrill at the apex may indirectly suggest the nature of the arrhythmia, by disclosing the presence or nature of organic heart disease.

HEART SOUNDS. The nature of an arrhythmia may be suggested by careful auscultation of the heart sounds, particularly at the apex. In *nodal rhythm*, the 1st sound tends to become louder each time that the atria and ventricles contract simultaneously. While in *paroxysmal atrial tachycardia*, the intensity of the 1st sound is constant from beat to beat, in *ventricular tachycardia* it may show a characteristic variation. In *atrial fibrillation and flutter* (particularly in the latter), the 1st sound tends to vary in intensity; in atrial fibrillation, the 2d sound may be absent, whenever the ventricular contraction fails to open the semilunar valves. In *atrial flutter*, extra sounds, due to audible atrial contractions, may be heard during diastole. In *first-degree AV block*, either the 1st sound becomes attenuated in intensity or an extra sound is heard in diastole because of early atrial contraction. In *second-degree AV block*, the 1st sound may be preceded by an atrial sound, a phenomenon never observed in SA block. In *complete AV block*, there is a slow but regular ventricular rate of 20 to 40 beats per minute, with variations in intensity of the 1st sound, which assumes at times a loud and explosive character, commonly referred to as *bruit de cannon*. Splitting of the 1st and 2d sounds may occur in *bundle branch block;* a diastolic triple rhythm in conjunction with pulsus alternans may also suggest this condition.

Special Methods of Clinical Examination. EFFECT OF EXERCISE. Acceleration of the pulse after exercise, atropine, or amyl nitrite, by its action on the cardiac arrhythmia, may supply information of diagnostic value. Although exercise tends to increase the cardiac rate in sinus tachycardia, it has no effect on the rate of paroxysmal tachycardia The *irregularity of the pulse in atrial fibrillation* is usually accentuated by exercise. Exercise has little or no effect on the ventricular rate of complete heart block, but may cause the ventricular rhythm of the Wenckebach type of AV block *to return to normal* In atrial *flutter*, the ventricular rate *may be suddenly doubled by exercise*, in most *rhythms*, the rise of rate tends to be gradual.

EFFECT OF RESPIRATION. Sustained and deep respiratory effort, whether inspiratory or expiratory, may terminate an attack of supraventricular tachycardia by *stimulating* the vagus nerve. The *simple maneuver* of holding the

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Type V: Irregular Rhythm with Slow Rate (Arrhythmic Bradycardia). (1) Sinus arrhythmia with sinus *bradycardia, (2) sinus* bradycardia *with sinus* pauses or SA block, (3) sinus bradycardia with extrasystoles (atrial, nodal, or ventricular), (4) nodal arrhythmia, (5) incomplete AV block with frequent dropped beats, (6) unstable AV *block,* (7) atrial flutter, with variable *and high degree* of block, (8) atrial fibrillation *with slow ventricular* response.

In the majority of cases, a clinical diagnosis is possible through careful interrogation and examination of the patient.

Type VI: Irregular Rhythms *with Rapid* Rate (Arrhythmic Tachycardia). (1) *Atrial* fibrillation, *(2) atrial flutter, (3) sinus tachycardia with multiple* extrasystoles, (4) AV dissociation (interference dissociation), (5) *paroxysmal* ventricular tachycardia

Clinical *diagnosis* is usually facilitated by (*a*) artificially raising the cardiac rate with exercise, atropine, or amyl nitrite, (*b*) careful palpation of the pulse, for timing of beats, "pulse deficit," and "dominant rhythm"; (*c*) study of the 1st sound for variations in intensity.

Type VII. Irregular Rhythm with Normal Rate. (1) *Sinus arrhythmia,* (2) normal sinus rhythm *with extrasystoles* (atrial, nodal, or ventricular), (3) SA block, (4) sinus pauses, (5) partial AV *block* with irregular dropping of beats, (6) Wenckebach type of AV block, (7) interference dissociation.

Clinical diagnosis is usually possible after a *careful interrogation* and examination of the patient.

Type *VIII. Clinically* Silent (Imperceptible) *Rhythms. This* group of arrhythmias is characterized by the complete absence, clinically, of all pulsatory phenomena, arterial, venous, and cardiac (1) *severe tachycardia* (e g, 1:1 atrial flutter), (2) *ventricular flutter,* (3) ventricular fibrillation, (4) paroxysmal tachycardia with ineffective systolic contractions (rare), (5) severe shock (e g, after coronary thrombosis), (6) long sinus pauses or cardiac standstill (e g, AV block with Stokes-*Adams syndrome).*

A careful study of symptoms and signs may furnish the required information, otherwise, an electrocardiogram is indicated for diagnosis.

CONCLUSION

Despite the apparent complexity of cardiac arrhythmias, careful history taking, physical examination, and simple methods of clinical investigation often make it possible to recognize the nature of cardiac arrhythmias without having recourse to specialized methods of instrumental investigation, such as electrocardiography.

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PART II: RATE, RHYTHM, AND CONDUCTION DISTURBANCES

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